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THE MONTH

DURING the last two years we have received an increasing number of queries from our readers on problems of heredity. This interest is not only a welcome sign of the extent to which the family doctor is keeping pace with advances in medicine, it is also a symbol of the changing face of medicine. To take one aspect of the problem, as Dr. C. O. Carter points out in his article on 'Heredity and congenital malformation', at the turn of the century when the infant mortality rate was over 100, the 5 per thousand whose death was due to a congenital malformation interested only the specialist. Now that little more than 20 per thousand live-born children are dying in the first year of life, the 5 per thousand who are still dying of congenital malformation naturally become a matter of concern to the general practitioner. It is because of this increasing importance of the subject, and the interest evinced in it by our readers, that we have decided to devote the symposium this month to 'Heredity and Hereditary Disease'. The subject is such a vast one that we have obviously had to be even more selective than usual. It is also highly technical, but our contributors have been at pains to discuss the problems allotted to them in language as free as possible from technicalities.

The Symposium

WITH that gift for hitting the right nail on the head—and hitting it hard—which he has shown on more than one occasion—the Duke of Edinburgh, in his presidential address to the Canadian Medical Association, drew attention to a problem which has been worrying many thoughtful members of the profession during recent years. This is the increasing incidence of what the Duke described as 'sub-health'. Naturally, in view of his audience, the figures he quoted were taken from the other side of the Atlantic. In brief, they were that in the United States 78 per cent. of the children submitted to a test for minimum muscular fitness failed to pass the test, as did 54 per cent. of children tested on first entering school. The comparable evidence from Canada was that 69 per cent. of children suffered from some sort of disability: 11 per cent. in excess of the average for all ages.

Physical Fitness

'The causes of this state of affairs', as the Duke pointed out, 'are widespread but not far to seek. Urban living, which will include 80 per cent. of

the population by 1980, lighter work, increased leisure, more sedentary occupations, altogether a higher standard of living and eating . . . . This very standard of living which we are so proud of, and which seems to be the goal of all the nations of the world, is having the same effect upon the community as a plaster cast has upon the muscles of the body'. The position in this country may not be as serious as on the other side of the Atlantic, but we cannot afford to be complacent. Apart from anything else, as the Duke commented, 'there is also a connexion between emotional instability, low level physical efficiency and delinquency. The lawless and the listless are equal menaces to society'. As industry persuades the machine to relieve the worker of more and more physical exertion and pays him more and more for doing less and less; as the motor industry persuades more and more citizens that it is simply 'not done' to walk; and as the Press persuades the public that only the champions in sport are of any consequence, there is a very real risk that we shall produce a race that is atrophied physically, as well as mentally and emotionally. The only section of the community that can resist this atrophic rot is the medical profession. Unless the doctors of the country do something about this they are failing in their duty to the community. As the Duke bluntly informed his Canadian audience: 'You cannot afford to ignore the facts and still maintain that you are in the least bit interested in health'.

Pony Riding for Polio

WHEN Mrs. Lis Hartel, of Denmark, with a post-poliomyelitis paralysis of both legs, hips and hands, won the silver medal in the Grand Prix de Dressage at the 1952 Olympic Games, widespread interest was aroused in the possible scope for pony riding in the rehabilitation of the physically handicapped—especially children. The idea was adopted with particular enthusiasm in Scandinavia, and in the summer issue of the *News Review* of the Central Council for the Care of Cripples, Miss Stella Saywell, M.C.S.P., gives an account of a visit she paid to Denmark and Norway to investigate what was being done in this way.

She has returned full of enthusiasm for the possibilities of this form of treatment. 'There is no doubt', she considers, 'that this form of treatment not only produces excellent balance and coordination of movement—but, perhaps more importantly, these handicapped children show much greater self-confidence and pride in themselves after very few lessons'. She does emphasize, however, that all treatments must be ordered by a medical practitioner and supervised by a physiotherapist. Most of the children whom she saw had either poliomyelitis or cerebral palsy. Typical of her comments is that on what she saw in Oslo: 'Their progress is astonishing: it was amazing to see children riding independently round the school, making small circles, changing reins across the school, halting and moving forward at the walk and trot. Some children were able to canter'. Practi-

tioners in this country will be interested to know that similar facilities are now available over here. On p. 234, Dr. Joan Bishop, for instance, draws attention to the fact that a weekly class for handicapped children is held at Bookham in Surrey. A more fascinating form of rehabilitation for children it is difficult to imagine, and it is to be hoped that facilities will soon become available in other parts of the country.

Children and Their Defects

On more than one occasion in his retirement Dr. Hugh Paul, the former medical officer of health for Smethwick, has turned his pleasantly caustic pen to good use by analysing official reports. In his latest excursion into this useful field (*Med. Offr*, 1959, **101**, 261) he analyses the tables in the report of the chief medical officer of the Ministry of Education for 1956 and 1957, which give the incidence of various defects found per 1000 periodic inspections in schools in various parts of the country. Some of the anomalies to which he draws attention take a great deal of explaining away and provide ample ammunition for the sceptic.

Why should Gateshead, for instance, have 152 visual defects requiring treatment (per 1000 periodic inspections) while Canterbury has only 11 and Oldham 10? Or why should Salop have 86 and Rutland only four? (In all cases the figures given are per 1000 periodic inspections.) Smaller, but still striking, differences occur in the case of squint—from 45.5 in Manchester to 0.5 in Halifax. Equally puzzling is the explanation of why the incidence of skin conditions requiring treatment should be 41.6 in Bradford and only 0.2 in Blackburn. The incidence of heart defects is equally curious: 54.9 in Barrow, 11.2 in Northampton and nil in half a dozen county boroughs including Wakefield and Warrington. Much is heard these days about the effect of environment upon lung disease, but why has Oldham an incidence of only 0.7 for lung defects requiring treatment, compared with 20.9 for Gateshead? Even the incidence of hernia varies: nine authorities report an incidence of nil, whilst Great Yarmouth heads the list with 3.2. It almost looks as if it might really be possible to explain anything by figures.

Hearts Across the Ocean

'The first successful transatlantic audiovisual transmissions of cardiac auscultation, including clinical data, rœntgenogram, electrocardiogram, and cardio-chart from New York to Paris and Rome and back have been accomplished'. So announces Dr. Arthur Briskier in a recent issue of the *Journal of the American Medical Association* (1959, **169**, 1981). The heart sounds were transmitted by short-wave radio through sound tapes, and a recording was made in Paris and Rome of the transmitted sounds. To check their accuracy in transmission they were immediately re-transmitted back to New York, so that within a few seconds the heart sounds crossed the

Atlantic twice, first to Europe and then back to America. With the heart sounds a visual record was transmitted by radiophotography, containing the clinical data on the patient, such as temperature and blood pressure, as well as a chest x-ray and electrocardiogram.

To the old-fashioned British doctor, this application of modern radio communication may appear to have little practical value. According to Dr. Briskier, however, it has 'such far-reaching applications, as cardiac consultations with specialists located anywhere in the world, particularly when the desired specialist is in a different continent than the patient'. To the harassed consultant of today this latest infliction of the scientist must appear much as the introduction of the telephone did to his predecessor. Even in the remotest of Innisfrees, peace will not come dropping slow if his days (and nights) are to be disturbed by ethereal auscultatory phenomena.

Chewing Gum

LAST year, according to *The Economist*, Americans spent $306 million on chewing gum, enough to provide them with 200 sticks of gum each. To provide this mass of gum required 150 million pounds of sugar, 50 million pounds of maize syrup, 20 million pounds of dried sapodillo syrup, 24 million pounds of rubber and resin, and 6 million pounds of chalk. What is not disclosed is how many million calories our American allies expended in this, their special national, version of chewing the cud. Surely, however, if there is anything in the law of hypertrophy, this mass chewing must have some effect on the size of the muscles of mastication. Curiously enough, no ambitious seeker after a promising project for an M.D., or Ph.D., thesis seems to have chosen this as a subject.

At least, such was the information we received when we took this matter up with our American colleagues a few years ago. Quite a number of articles had been published on chewing gum, but most of them dealt with it as a vehicle for drugs. Others dealt with the effect on oral temperature, the teeth and gastric secretion. The most interesting of these was the one which reported that gum chewing produces a 'physiologic' rise in oral temperature of from 0.4° to 1.2°F., a state of affairs which it described as 'chewing gum fever'. None, however, dealt with the effect on the muscles of mastication, although our distinguished contemporary, the *New England Journal of Medicine*, has expressed the view that gum chewing 'gives to each citizen of the United States, like Father William, a muscular strength to his jaws that will last the rest of his life, without going to the trouble of arguing at the law'. Perhaps one day some enterprising contributor will give us the privilege of publishing an article on 'The effect of gum chewing on American physiognomy'.

PRINCIPLES OF HEREDITY

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WHEN the older clinicians spoke of hereditary and of familial diseases they were groping towards the present-day distinction between dominant and recessive forms of genetically determined affections. By hereditary affections they meant disorders transmitted from one generation to another and erroneously included congenital syphilis in this group—erroneously for the child with congenital syphilis does not suffer from a genetically determined affection, but is a survivor from a disturbance in embryonic life which was sufficiently severe to damage but not severe enough to kill. The pathology of the embryo and the fœtus is a field that still waits to be explored. That it is significant is obvious from the high incidence of failure of conception, of miscarriage, of stillbirth and of congenital defects. Hereditary factors are only one aspect of this unexplored terrain, and—as the relatively recent work on maternal rubella and toxoplasmosis has shown—congenital syphilis is only one of the maternal infections that can damage the embryo. That many other factors also come into play is obvious from studies on the Rh factor and other aspects of auto-immunization.

The older clinicians were likewise on uncertain ground in their category of familial diseases, by which they meant the occurrence of an affection in a sibship derived from normal parents. Apart from the fallacy of latent parental syphilis, often called in as an easy explanation, there was no clear appreciation of the fact that a family group has an environmental background in common: thus, rickets affecting a sibship was not genetically determined, but the result of malnutrition which the sibship had in common. In contrast, it was not realized that familial diseases in the present-day sense —recessive disorders—could occur as isolated cases (as when the sibship is small, or because of the chance occurrence that only one in a large sibship, and not the expected 1 in 4, would be affected).

THE MENDELIAN RULES

No clear understanding of the criteria that define hereditarily determined disease was in fact feasible until Mendelian principles came to be applied in genetics generally, and in pathology in particular, at the beginning of the century. The Mendelian rules are simple and as essential to medical genetics as Koch's postulates are to bacteriology. In discussing the principles of hereditary disease, four distinct things need to be considered: (1) modes of inheritance, (2) the pathology and variety of genetically determined diseases, (3) the likely scope of heredity in medicine, and (4) therapeutic possibilities.

If a physiological characteristic such as stature is considered in a group of people, it is found that all heights between two extremes are represented: i.e. there is variation of a continuous type. In contrast, disease represents a sharp antithesis to the normal; in biological terms it is a discontinuous variation. Whilst in man and higher animals physiological characteristics generally show continuous variation, in the lower forms of life they are

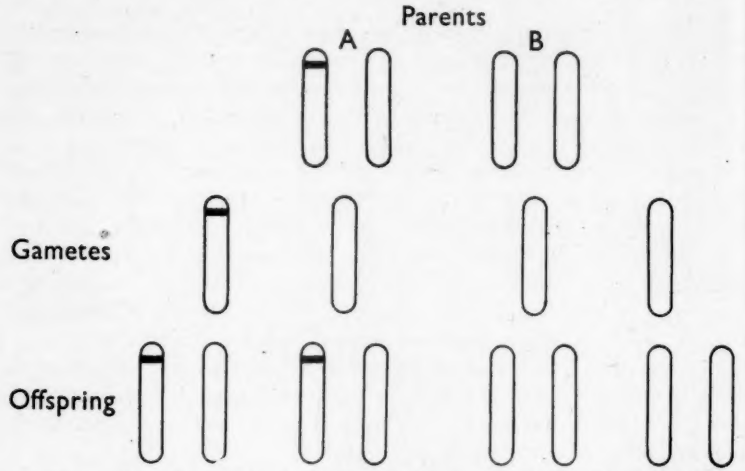

FIG. 1.—Inheritance when one of the parents carries a single pathogenic gene.

often discontinuous. In studying tall and dwarf pea-plants, Mendel in his classical experiments found that no matter what crosses were carried out, the two types, tall and dwarf, always remained distinct: intermediate forms did not occur. Whilst all lines of dwarf plants bred true—giving only dwarfs —only some lines of tall plants bred true and others threw up dwarfs as well as talls. Such occurrences were known to the older biologists, who regarded them as 'sports'. Mendel's immense contribution was to count his plants and to show that there were distinct ratios as between the different plants seen from different crossing experiments. To explain his observations he made a number of assumptions which may be summarized thus:—

(1) A given bodily character is determined by the joint action of two units of hereditary matter.

(2) These units may or may not determine identical somatic features or characters: i.e., may or may not produce the same effect.

(3) These units are indivisible and do not blend. They separate from one another, or segregate, at the formation of gametes (Mendel's *law of segregation*).

(4) In fertilization, the combination of any pair of units of hereditary matter is a chance reassortment (Mendel's *law of independent assortment):* that is, each of the two units contributed by one of the parents has an equal chance of meeting either of the two units contributed by the other parent.

(5) This chance reassortment may bring together units determining identical or dissimilar characters.

(6) In this mechanism of segregation and assortment there is combination and recombination of the units of inheritance, but never any blending.

(7) When two units determine two dissimilar characters, one unit only is generally manifest: it is *dominant* to the other unit, which is designated as *recessive*.

(8) Where more than one character is under consideration, the units determining the different characters are subject to the law of independent assortment (except in special circumstances discussed later.) As an example yellow wrinkled peas may be given; dependent upon the chances of assortment, yellowness and wrinkling may or may not be associated in the same pea.

The units or factors postulated by Mendel are the genes of present-day genetics. It is a moot point whether they are visible under the microscope,

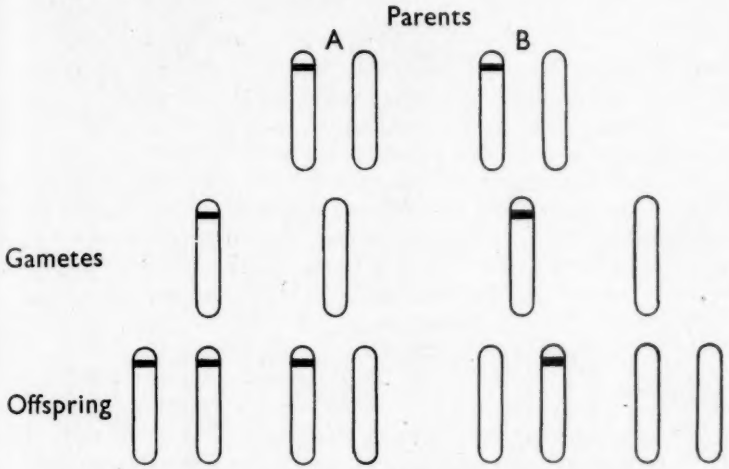

FIG. 2.—Inheritance when both parents carry a pathogenic gene.

but there is no dispute over the chromosomes which carry them. These are readily studied and much of the behaviour attributed to the genes can be observed as actual events in the maturing germ cells in which the chromosomes can be seen to segregate and recombine. This is the 'dance of the genes' in action, and applies to the discontinuous variations with which human pathology is mainly concerned.

THE 'DANCE OF THE GENES'

Accepting these postulates, the simple diagram in figure 1 shows the sequence of events with a single gene for a pathological feature. If the gene is dominant, A is affected and 50 per cent. of his children are also affected. If the gene is recessive, i.e. normalcy is dominant, neither A nor any of his offspring are affected, but those carrying the gene (A himself and 50 per cent. of his offspring) are 'carriers'. In this example the pathogenic gene was carried by only one parent, A. If, however, both parents (A and B) carried

the pathogenic gene, then the situation shown in figure 2 would arise. Here 50 per cent. of the offspring repeat the pattern shown by their parents, but 25 per cent. have two pathogenic genes on their paired chromosomes, and 25 per cent. carry no pathogenic gene at all. The clinical manifestation would again depend upon whether the gene is dominant or recessive. If recessive, neither A nor B would show the affection, nor would the 50 per cent. of the children who repeat their pattern, nor, of course, would the 25 per cent. with normal genes, but the 25 per cent. with two recessive genes would be affected. This is the classical situation of normal parents, both

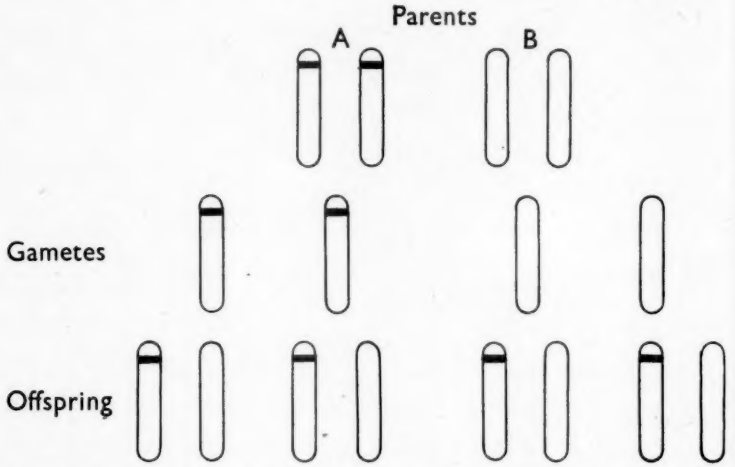

FIG. 3.—Inheritance when one parent carries a pathogenic gene on each of a pair of chromosomes.

carriers (and sometimes related, as relatives are more likely to possess similar genes), having an affected child, the actual proportion of affected to normal being 1 in 4 (1 affected, 2 carriers, 1 normal). Exceptionally, the situation in fig. 2 applies to dominant genes: here both parents would be affected and 75 per cent. of their children (the 25 per cent. with two dominant genes being probably more severely affected or stillborn).

One further common situation may occur, as shown in figure 3. A has two pathogenic genes and B is normal. All the children are genetically carriers. Whether they would be affected clinically depends upon whether the gene is dominant or affected. In the rare event of A having two dominant genes, all the children would of course be affected. (Assuming that A carried two recessive genes, 50 per cent. of his children would be affected if B were a carrier—as the reader can see for himself by making a simple diagram.)

To sum up:—

(1) The pattern of combination and recombination of genes—the

dance of the genes—is the same whether the gene is dominant or recessive.

(2) A single recessive gene is clinically silent, a single dominant gene is clinically manifest.

(3) The distinction between dominant and recessive is fundamental clinically. In dominant affections only one parent need be genetically affected. In recessive affections both parents, themselves normal, contribute to the affection in the offspring.

(4) These simple schemes explain how normal parents come to have affected children and how affected parents can have normal children.

SEX-LINKAGE

In discussing basic modes of inheritance one important special case needs to be considered—sex-linkage. The number of chromosomes varies considerably as between different species. In man there are 23 pairs: 22 of these pairs are indistinguishable in the two sexes and are known as autosomal chromosomes; the 23rd pair is the sex-determining pair of chromosomes. In the female the two chromosomes in the pair are identical and are known as X-chromosomes; in the male one chromosome is similar to the X-chromosome, but the second one is shorter and is known as the Y-chromosome. Genetically the female is therefore XX and the male XY. Figure 4 shows how sex affects the manifestation of a disease carried by the X-chromosome. In figure 4a the pathogenic gene is carried by the father. Irrespective of whether the gene is recessive or dominant it will show itself clinically, as there is no normal gene to suppress its manifestation. This affected man will pass on his X-chromosome with the pathogenic gene to all his daughters, and will pass on his Y-chromosome to his sons. The sons are therefore normal for they have no X-chromosome carrying the pathogenic gene; their X-chromosome is derived from the mother. The daughters are all carriers for they have one normal X-chromosome (from their mother) and one X-chromosome carrying the pathogenic gene from their father. If the gene is recessive—as it generally is—the daughters do not manifest the affection, but will pass it on to 50 per cent. of their sons, as can be seen from figure 4b. (In the rare event of the gene being dominant, the daughters of an affected man would, of course, show the affection.) The classical examples of recessive sex-linkage are colour blindness and hæmophilia; where men are affected, their sons are normal, and their daughters are carriers; 50 per cent. of sons born to their daughters show the affection, whilst 50 per cent. of the daughters would again be carriers (figure 4b).

In any particular sibship an isolated case of a recessive sex-linked affection may occur without obvious family background, as the pathogenic gene may have been transmitted by two or even three generations of carrier women. The Y-chromosomes carry few genes. A pathogenic gene would, of course, be transmitted exclusively from father to son—a rare event.

SOME IMPORTANT CLINICAL ASPECTS

Apart from these fundamental rules on segregation and recombination, there are several aspects of gene action that are important clinically. These may be summarized briefly.

(1) *Pleiotropic effect.*—Few, if any, genes have just one effect; they in-

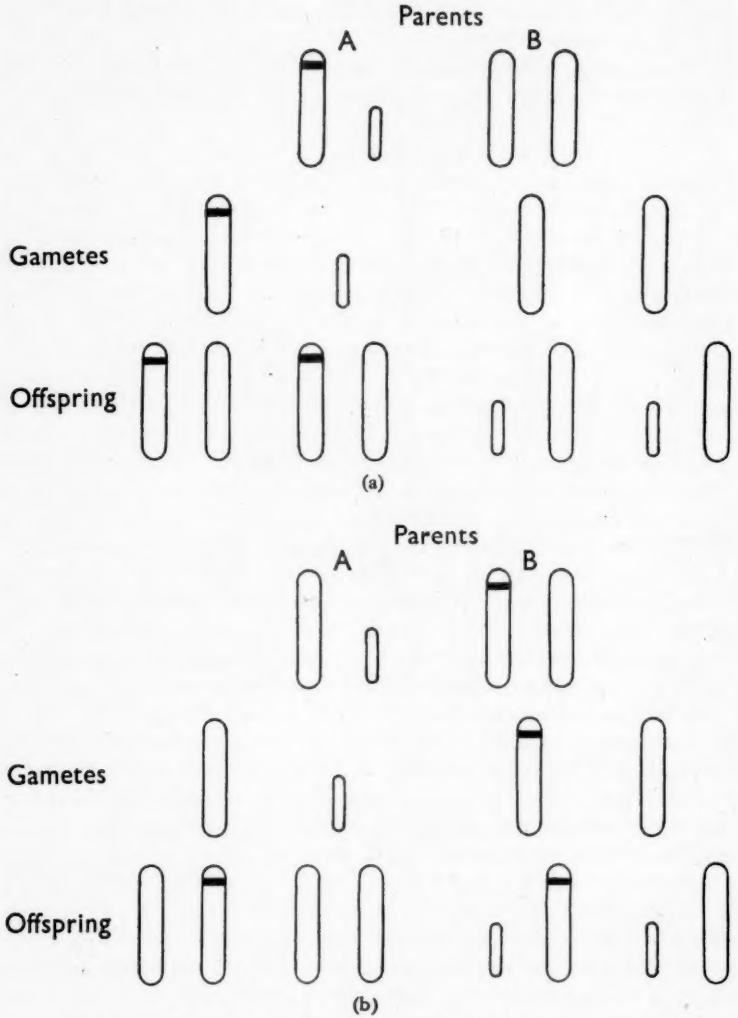

FIG. 4.—Inheritance of a pathogenic gene carried on the X-chromosome. In fig. 4a the gene is carried by the father, and in fig. 4b by the mother.

fluence several, and possibly many, characteristics. The classical syndromes are a case in point. The pathogenic gene which determines the Laurence-Biedl syndrome influences not only the development of the brain, but also that of the retina, skeleton and genital tract, giving in consequence the bizarre combination of mental deficiency, obesity, retinitis pigmentosa, polydactyly and hypogenitalism. Not all patients with the Laurence-Biedl syndrome show the complete picture. This leads to a second aspect: expressivity.

(2) *Expressivity.*—The pathogenic action of a gene need not manifest itself fully. As a result, whilst there is a striking resemblance between different patients suffering from the same hereditary disturbance, there are also considerable variations depending upon the fact that the gene is not fully 'expressed', possibly because of the effect of other genes—'modifying genes'. The action of the gene may, in fact, be entirely suppressed, giving the appearance of irregular dominance in some cases: i.e. a pathogenic gene is present but its manifestations are suppressed in the particular bodily environment of the particular patient, but not in the different environment of an offspring to whom the gene has been transmitted.

(3) *Linkage.*—Each gene lives not by itself, but in a community of genes. Generally a pathogenic effect is the result of one abnormal gene, but this pathogenic gene, being placed in a particular chromosome, will of necessity be transmitted with a block of other genes on that chromosome (except for special conditions like crossing over); it may come about that two pathogenic genes will normally be transmitted together (linkage of pathogenic genes). Linkage, of course, also occurs with non-pathogenic genes such as genes determining particular blood groupings. It is for this reason that blood groupings can be used as markers for particular chromosomes.

(4) *Homozygotes and heterozygotes.*—The essential distinction between recessive and dominant affections, as has already been seen, is that with a recessive affection the patient carries two pathogenic genes: one on each of a pair of chromosomes (this is the *duplex* or *homozygous* condition and holds good except for the special situation with X-chromosomal inheritance). In dominant inheritance the pathogenic gene is carried on only one chromosome (the *simplex* or *heterozygous* condition).

(5) *Carriers and intermediate inheritance.*—Strictly speaking the term carrier applies to an individual who carries a pathogenic gene irrespective of whether or not the gene shows clinically. It is generally restricted, however, to individuals who possess a pathogenic gene but do not show it: all the offspring of a person suffering from a recessive disorder, some of the daughters of a woman carrier of a sex-linked affection, a person carrying a dominant gene not expressed, i.e. the carrier of an irregular dominant gene, are all carriers in the restricted sense. When, theoretically, both carriers and genetically normal individuals may occur in a given family it is a matter of considerable importance to be able to distinguish between these two types

of clinically normal people. This, however, is not always possible. One procedure which is particularly useful—when applicable—is based upon the recognition that many diseases are neither simply recessive nor simply dominant, but intermediate, and that individuals carrying genes with an intermediate mode of inheritance may show mild manifestations: variations from the normal which are not strictly pathological, but have been classified in the past as physiological variations. A particularly striking example is the marked sheen seen in the fundus of a carrier of sex-linked retinitis pigmentosa; such carriers have normal sight, but the ophthalmoscope will distinguish between a carrier who will transmit the affection and her normal sister who will not.

PATHOLOGY AND VARIETY OF HEREDITARY DISEASE

Cleft palate and Huntington's chorea are both hereditary affections, but differ markedly in the fact that the first is a congenital defect and the second develops in middle age in an individual previously normal. These two affections exemplify in broad outline the two major groups of hereditary disease: the congenital abnormality and the abiotrophic disorder.

The understanding of a *congenital hereditary defect* calls for a much deeper understanding than we now possess of normal development and its aberrations. It is clear that in general terms two types of disturbance may occur. In one there may be arrested development, giving at birth a feature that is normal at an earlier stage of development; thus, hare-lip and cleft palate do in fact represent a normal appearance in embryonic life. The other type represents something outside the normal range of development: thus the opaque lens of congenital cataract, transmitted from generation to generation, does not find its counterpart in normal development. Affections of this type come close to the pathological deviations seen with disturbances of environmental origin damaging an embryo—embryopathies.

The *abiotrophic defect* presents an even more complex problem. An older generation regarded abiotrophic disorders in rather mystical terms: failure of vitality in a fully developed tissue. Sir James Paget—and later Sir William Gowers who popularized this concept—stressed the similarity to premature senescence. Such views raise difficult questions on the nature of senescence and of life itself. Fortunately the position is rather simpler. Abiotrophic disorders of different systems occur in animals no less than in man, and, judging by the histological appearances in strains of mice, rats and the Irish setter affected with a disorder allied to retinitis pigmentosa, the retina, though fully functioning at birth, is not fully developed histologically. The final stages of differentiation are lacking and abiotrophic disease in these animals is nothing less than degenerative changes in an incompletely developed retina—a jerry-built retina to use a colloquialism. In fact the abiotrophic disorder is the mildest of congenital defects, running its course in post-natal life in contrast to the classical congenital defects which have

run the whole of their course in intra-uterine life. Presumably most abiotrophic defects, no less than most congenital defects, represent arrested development with secondary degenerative effects, differing only in the time when these degenerative effects set in.

The sharp antithesis between the congenital and abiotrophic defect is therefore no longer valid, although there are still considerable problems in the understanding of the nature of hereditary disorders. At the beginning of the century Garrod's important studies on inborn errors of metabolism pointed to the possibility that hereditary disorders are determined by chemical abnormalities. It would now seem likely that these chemical defects are themselves determined by failure of enzyme processes. Apparently a succession of enzyme processes are called into being during the course of development, each one carrying forward normal development, and failure of one or other of these intermediate and ultimate enzyme processes

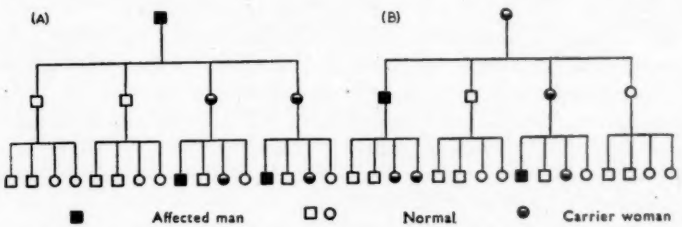

FIG. 5.—Schematic representation of transmission of pathological and carrier states in intermediate sex-linkage in idealized families of four children. (A) Transmission by an affected man. (B) Transmission by a carrier woman.

In pedigree (A) an affected man has only carrier daughters, and these pass the affection on to 50 per cent. of their sons. In three generations comprising an idealized family group of 21 individuals, there are therefore three affected men.

In pedigree (B) a woman carrier in an identical group has an affected son and a carrier daughter. In the third generation only one boy will be affected. In this idealized family group also comprising 21 individuals there will therefore be two affected men in three generations.

determines clinical abnormality. This clinical abnormality may be mild as in congenital pentosuria, or severe because of associated defects as in congenital phenylketonuria with its associated mental defect. Some of these metabolic failures may be lethal in infancy as in Tay-Sachs' disease; others may not become apparent until later in life as in diabetes mellitus. The significant thing in these developments is that hereditary disease is no longer an Eleusinian mystery, but part of normal scientific inquiry.

THE LIKELY ROLE OF HEREDITY IN MEDICINE

The hereditary diseases are seen in every branch of medicine. At the very least they account for 20 per cent. of all cases of blindness. In the cardiovascular disorders a hereditary factor is clearly seen in many cases of essen-

tial hypertension and of coronary occlusion. In disorders of the central nervous system affections such as Friedreich's ataxia and the muscle dystrophies are genetic in origin. Whether there is a hereditary factor in malignant disease as a whole is a matter of dispute, but there is no question about a marked hereditary background in some tumours such as retinoblastoma, neurofibromatosis and glioma. In orthopædics, the genetic factor looms large as it does in the metabolic disorders and in dermatology; and in the mental disorders the role of inheritance is not insignificant.

The complexity of the recognized modes of inheritance explains why an apparently negative family history is not conclusive evidence against a reasonable assumption on clinical grounds that a particular patient suffers from a hereditary disturbance. Figure 5 shows schematically how difficult it is under normal conditions to establish the presence of a sex-linked affection. Obviously a 'sporadic' case of hæmophilia is no evidence for a non-genetic type of the disorder. Many similar difficulties could be cited, and it is clear that in clinical practice a genetic etiology may have to be assumed on the clinical appearances, just as infection and a particular infecting organism have occasionally to be assumed in spite of negative bacteriological findings. Nonetheless, such negative considerations must be used with extreme caution. With a fuller appreciation of the difficulties inherent in the genetic diagnosis of disease, many disorders previously not suspected as genetic in type, have come to be regarded as such. Polyposis of the colon, Dupuytren's contracture, the leukæmias, rheumatoid arthritis and many other affections of obscure origin have all been shown to possess a genetic background. Even more significant has been the recognition that in many disorders both genetic and environmental factors are operative jointly. Tuberculosis is undoubtedly an infection, and family groups affected could be readily explained as the result of exposure to the same infective environment. Yet some families are more prone than others to become infected and under experimental conditions it is possible to rear rabbits particularly prone and particularly resistant to tuberculous infections. Even the susceptibility to colds or to sinus infections may be genetically determined, for some families are more prone than others under similar environmental conditions to develop such infections. It is known that different types of physique determine a difference in proneness to particular disorders: the lean and hungry look of the potential duodenal ulcer patient is an example, and physique itself is genetically determined. It is clear that some hereditary diseases will manifest themselves under all environmental conditions, and others only in certain favourable circumstances. The classical hereditary disorders are merely the most marked and most easily recognized of a much larger group.

Present-day genetics with its increasing complexity is constantly enlarging this already substantial group. Such an affection as Turner's syndrome—marked sexual infantilism in girls, who also show various congenital ab-

normalities such as webbing of the neck and cubitus valgus, all apparently secondary to ovaries that are either completely absent or rudimentary—could not readily be visualized as hereditary in character; likewise the evidence for a hereditary factor in mongolism has not been very convincing. The demonstration during the last few months that both these affections, and possibly others, can be determined by abnormalities in the chromosomes as distinct from the genes has opened a wide field, extending the potential scope of genetics in medicine beyond anything imagined even in recent years. The problem today is not so much to justify the genetic approach to clinical difficulties, but to maintain a sense of proportion so as to avoid the mistakes made by contemporaries of Pasteur and of Koch who thought of all disease in terms of bacteria. Traditionally medicine has stressed the constitutional aspect of disease; in recent centuries—possibly in consequence of the break-up of the village community and the emergence of the large towns of an industrial age—infection has dominated pathology. Present-day genetics suggests that both views were only partial truths. A new pathology is emerging: the synthesis of constitution—including genetic constitution—and environment.

THERAPEUTIC POSSIBILITIES

A hundred years ago bacteriology was largely an academic subject with little therapeutic promise. The antibiotics that are inimical to bacterial life without affecting the host were not even a dream until very much later—when postulated by Ehrlich. Genetics today is not altogether devoid both of immediate therapeutic possibilities and therapeutic potentialities. Whilst surgical treatment can correct genetically determined deformities, and dietetic control and insulin can keep in check diabetes mellitus—generally a recessive affection—the specific correction of hereditary disorders must await a fuller understanding of the underlying mechanism that produces these disorders. It is likely that these mechanisms are chemical in nature and it is possible that, even if understood, it may not be possible to develop substitution therapy when a particular enzyme system is lacking. This, however, is a matter for the future. For the present there is this immensely heartening fact: Nature is constantly suppressing the manifestation of hereditary disease, as shown by irregular dominance and the appearance of partial manifestation of hereditary disorders. The history of therapeutics is largely the record of exploiting such clues.

HEREDITY AND CONGENITAL MALFORMATIONS

By C. O. CARTER, B.M., M.R.C.P.

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When, as in the early part of the present century, more than 100 live-born children per thousand died in the first year of life, the 5 per thousand whose death was due to a congenital malformation interested only the specialist. Now that little more than 20 per thousand live-born children are dying in the first year, the 5 per thousand who are still dying of congenital malformations naturally become a matter of concern to the general practitioner and the public health officer. In addition to causing about 1 in 4 of infant deaths, congenital malformations make a considerable contribution to infant and child morbidity. About 1 child in 50 is born with a serious or moderately serious malformation.

Some of the commoner individual severe malformations in Western European populations are: anencephaly, frequency about 2 per thousand; meningocele and meningo-myelocele about 2 per thousand; mongolism about 2 per thousand; congenital malformations of the heart of all types about 3 per thousand; pyloric stenosis (perhaps not strictly congenital) about 4 per thousand; congenital dislocation of the hip (not all strictly congenital) about 1 per thousand; hare-lip, with or without lateral cleft palate about 1 per thousand; Klinefelter's syndrome about 1 per thousand. More common, but less serious are: hypospadias, about 3 per thousand; undescended testes about 3 per thousand; club foot about 6 per thousand; polydactyly about 6 per thousand.

THE CAUSES OF MALFORMATIONS IN GENERAL

Not so long ago, many people thought of congenital malformations, just because they were congenital, as nearly all being due to hereditary factors. Then with the discovery that rubella in the first three months of pregnancy could cause congenital malformation, and the discovery that malformations can be produced in animals by vitamin deficiency, hormone injection, low oxygen pressure and other external agents, many came to think of most malformations as due to environmental factors.

Taking malformations as a whole, neither the extreme genetic nor the extreme environmentalist view is correct. For most of the commoner malformations, the evidence, incomplete though it is, suggests that for a malformation to develop it is necessary to have both a genetic predisposition and some environmental trigger. The genetic predispositions appear to be specific; there is a predisposition to develop a particular malformation, or

one of a group of closely allied malformations. There are, however, malformations which, for practical purposes, are entirely genetically determined and others which, for practical purposes, are entirely environmentally determined. One of the best methods of making a preliminary estimate of the importance of genetic factors in the causation of any particular malformation is through the study of the co-twins of affected children. If the malformation is purely genetically determined, identical co-twins of affected children will always also be affected and fraternal co-twins much less often affected. In the case of mongolism, for example, there is no known exception to the rule that an identical co-twin is always also a mongol. If the malformation is purely environmentally determined, identical co-twins will no more often also be affected than fraternal co-twins. This is probably the case for some at least of the malformations of the heart. If both genetic and environmental factors are concerned then identical co-twins of patients with the malformations will also be affected with a frequency much below 100 per cent., but significantly more often than are fraternal co-twins. This last situation has been found, for example, with congenital dislocation of the hip and club-foot. It also occurs, though the numbers studied are too small to be highly significant, with pyloric stenosis and hare-lip.

Twin studies, however, are only a preliminary step, and to discover something of the mechanism of inheritance family studies are needed and it has been possible, very recently, to supplement these in one or two instances by direct study of the chromosomes.

PURE GENETIC DETERMINATION

At present it is possible to recognize two main classes of genetic change which so disturb development that a malformation is induced in almost all environments. The first of these are chromosome mutations in which a large fragment or even a whole chromosome is involved. The second are found in gene mutations in which only a small segment of a chromosome is involved, either lost or undergoing internal change at the molecular level.

CHROMOSOME MUTATION

The only malformations in man where a chromosome mutation has been recognized by direct cytological examination are the syndromes known as mongolism and Turner's syndrome, although Klinefelter's syndrome might also be included if the testicular dysgenesis is regarded as a congenital malformation. The discovery this year in France, and soon after independently in England, that mongols have 47 chromosomes, instead of the usual 46, explains the facts already known about mongolism. These were: the apparently 100 per cent. concordance of identical twins for mongolism, the two out of four instances in which mongol women have given birth to mongol children, the rarity with which brothers and sisters of mongols are also mongols. The greatly increased risk of mongolism as the mother's age increases suggests that the non-disjunction of the twenty-second or twenty-

third chromosome, which results in its being present in triplicate instead of duplicate in mongolism, must usually occur in ovum rather than sperm formation. In Klinefelter's syndrome the chromosome abnormality has been shown by British cytologists to be an extra sex chromosome, these children having two X-chromosomes as well as a Y-chromosome. In Turner's syndrome, in contrast, the patients have one sex chromosome missing and have only a single X-chromosome. Here, in addition to ovarian dysgenesis, there may be severe associated malformations, mental defect, deafness, coarctation of the aorta and renal abnormalities. With these two syndromes, as with mongolism, it is rare to find other relatives affected. Again as with mongolism there would probably be a considerable risk that any children of patients with Turner's and Klinefelter's syndromes would be affected, but it is doubtful at present whether these patients are ever fertile.

Parents of a mongol child who ask for the risks that a later child will be affected in the same way, can be told that the risk is small. The risk, in fact, is probably somewhat higher than for any woman of the same age, but the increase is probably not more than twice the random risk. There are no large-scale family studies of Turner's and Klinefelter's syndromes on which to base an estimate of the risks, but here, too, the risk of a later child being affected in the same way is probably small.

GENE MUTATIONS

Numerous malformations are known due to gene mutations, but most of them are rare, and only one, fibrocystic disease of the pancreas, has a frequency (about 1 in 2000 births) comparable to that of mongolism and Klinefelter's syndrome. Nevertheless, it is important to recognize these conditions known to be essentially due to mutant genes, since it is in these conditions that there may be a high risk to subsequent children.

Taking first *dominant mutant genes*, some examples of malformations caused in this way are:—

Skeletal system
Achondroplasia (fig. 1): many instances, some are non-genetic
Cleidocranial dysostosis
Craniofacial dysostosis
Brachydactyly
Ectrodactyly

Vascular and lymphatic system
Milroy's disease: many instances
Sturge-Weber's disease: many instances

Joints
Familial joint laxity
Ehlers-Danlos syndrome

Skin
Congenital ectodermal dysplasia: many instances, some anidrotic

Eyes
Congenital ptosis: many instances
Congenital cataract: many instances
Aniridia: most instances

With these conditions due to dominant genes, provided that the diagnosis is well established and with due regard for the possibility that some forms of the condition may be caused in other ways, it is not difficult to advise on the risks to further children in these families. When an affected child is born to normal parents, it is probable that a fresh mutation has occurred and there is little risk of the parents having another affected child. If, however, an affected individual has a child there is a 1 in 2 risk that the child will be affected. For example, although there is evidence that non-genetic types of achondroplasia may occur, particularly among those who die young, it is most unusual for a second child to be born to normal parents, but there is a risk of about 1 in 2 for the children of affected individuals.

FIG. 1.—Achondroplastic dwarfism in mother and son.

Malformations due to *recessive mutant genes*, where the child is not affected unless he receives the mutant from each parent include:—

Skeletal system
Morquio's disease
Central Nervous system
Congenital deafness: most instances
Infantile progressive muscular atrophy
Skin
Ichthyosis congenita
Epidermolysis bullosa dystrophica (severe form)
Eyes
Buphthalmos: many instances
Congenital subluxation of the lens with ectopic pupil
Mucus and sweat glands
Fibrocystic disease of the pancreas
Ductless glands
Pseudohermaphroditism due to congenital adrenal hyperplasia
Syndromes
Ellis-Van Creveld syndrome
Fanconi's anæmia syndrome
Micropthalmos with mental defect
Mental deficiency with congenital cataract and spino-cerebellar ataxia

Giving parents, who have had one child with any malformation determined in this way, advice on risks to further children, is once again straightforward provided that the diagnosis is well established. Once parents have had one child with one of these conditions, the risk of further children being malformed in the same way is 1 in 4. The unaffected brothers and sisters of the patient, however, and even the patient himself if he or she survives, are not liable to have affected children unless they are unlucky enough to marry, unwittingly, someone who carries the same recessive gene. This is not such a remote risk as might be thought, little less than 1 in 20 of the population must be carrying the gene for fibrocystic disease of the pancreas.

There are also malformations due to recessive mutant genes on the unmatched section of the X-chromosome. These include:—

Muscles
Duchenne type of muscular dystrophy

Skin
Anidrotic ectodermal dysplasia: most instances
Megalocornea: most instances

Kidney
Nephrogenic diabetes insipidus: only partially recessive

There is good reason why these conditions due to mutant genes should be rare. Gene mutation, in contrast to the chromosome mutations previously described, are rare events, and the frequency of these conditions will usually have a close relationship to the mutation rate. The exceptions, such as fibrocystic disease of the pancreas, probably depend for their relatively high incidence on some extra degree of fitness, present or past, possessed by the heterozygous carriers of the gene.

The other common malformations all appear to have mixed genetic and environmental origin.

PART-GENETIC AND PART-ENVIRONMENTAL CAUSATION

There is good evidence from twin and family studies that the remainder of the more common severe malformations mentioned in the first paragraph of this article, have a mixed genetic and environmental causation. These conditions are anencephaly, meningocele and meningo-myelocele, congenital malformations of the heart, pyloric stenosis, congenital dislocation of the hip, and hare-lip with or without lateral cleft palate. With these conditions it is impossible to be precise about the genetic mechanisms or about the risks to further children in the families. Nevertheless, in some instances empirical risks are known which are of some use in answering parents' questions.

The major *central nervous system malformations* have a similar embryological origin in that they are all due to a failure of some part of the neural tube to close. They are also linked genetically since parents who have had one child with anencephaly have an increased risk of having a second child with meningocele or meningo-myelocele, as well as an increased risk of

having a second child with anencephaly. Grouping these two conditions together, it may be said that once parents have had one child with one of these malformations, the risk of the next child being affected in the same way is of the order of 1 in 25. The risk is ten times as great as the random risk, but still not a very high risk and one that should be seen in the perspective of the 1 in 50 risk of some fairly serious malformation or other occurring in

FIG. 2.—Hare-lip (repaired) in a man and his two children.

any pregnancy. An increased risk of this order does not necessarily imply genetic predisposition, but such predisposition is the most straightforward explanation. That environmental factors are also concerned is shown by two interesting recent findings from the valuable Scottish data on still-births. One is that anencephaly occurs significantly more often in the lower socio-economic groupings. This is the only malformation whose incidence is known to be affected by social factors. The other is that anencephaly occurs more often in children born in winter than in those born in summer, the peak months being December and January. Another recent finding for anencephaly is that there are most striking regional differences in the frequency with which it occurs. The British Isles, particularly Ireland and Scotland, show high frequencies, whilst in central Europe the malformation is rare. The rare women who have had two children with this type of malformation, and ask for information on the risks for further children, pose a difficult problem. A small personal series of the author's indicates that the risk is definitely higher than 1 in 25, but still better than 1 in 5.

Congenital malformations of the heart obviously comprise a mixed group of disorders, probably of differing etiology. Maternal rubella is, of course, one cause, but accounts for only a small fraction of all malformations of this type. The small-scale twin studies so far available indicate that the proportion of identical co-twins of patients also affected is low. Family studies, however, suggest a small but definite increase in the risk for later children: the risk is of the order of 1 in 50. When a second child is affected, too, the malformation tends to be of the same kind as in the first affected child. As

the diagnosis of cardiac malformations becomes more precise because more and more affected children undergo operation, it will become possible to assess the risks for each individual type of malformation.

Family studies show that cases of *hare-lip* (fig. 2) and *cleft palate* fall into groups with distinct heredity. One group consists of patients all of whom have hare-lip, but who may have an associated lateral cleft palate. This is

FIG. 3.—Identical twin boys and their brother treated for Hirschsprung's disease by recto-sigmoidectomy.

the common form with a frequency of about 1 in a 1000 live-births. The second group comprises patients with a central cleft palate of varying degree and no malformation of the lip; this is less common, with a frequency of only about 0.4 per 1000 live-births. In the hare-lip group all degrees of the malformation appear to have a common genetic predisposition since in the same family one may find patients with a minimal degree of uncomplicated unilateral hare-lip, and patients with severe bilateral hare-lip and cleft palate. Twin studies show that only about a quarter of the identical co-twins of patients are also affected. This suggests that only about a quarter of those with the genetic predisposition are clinically affected and environmental factors must also play a part in causation. The exact mechanism of inheritance is not established. The simplest explanation that fits the family findings is, perhaps, that a rather common recessive gene is concerned, but that only about a quarter or a fifth of those homozygous for the gene develop the condition. An excellent large-scale family study from Denmark, supplemented by a personal series, makes it possible to give empirical risks to parents who seek advice. If two unaffected parents have had a child with the abnormality, the risk of a further child having the malformation is about 1 in

20. If, however, one of the parents of an affected child has himself or herself some degree of the malformation, however minor, the risk to a further child rises to about 1 in 10. If an affected individual who has had no children, asks about risks, he may be told that the risk to his children is relatively small, about 1 in 50, but once an affected child has been born the risk rises considerably to about 1 in 7. The probable explanation here is that the birth of an affected child implies that the patient has been unlucky enough to marry a spouse who also carries the gene.

Pyloric stenosis is also a condition in which probably only a minority of those with a genetic predisposition develop clinical symptoms. When two parents, themselves unaffected, have had a child with the condition, the risk of further children having the same condition is about 1 in 12 for boys and 1 in 50 for girls. The risk is probably significantly increased if one parent, particularly the mother, also had the condition, but the numbers yet known of such families are small. The risk to children of affected individuals is of the same order as to brothers and sisters, but as new families accumulate it appears that the risk to the children is considerably higher where the patient is the mother.

The last common condition, *congenital dislocation of the hip*, has not yet been fully studied genetically. An excellent German twin study showed that the risk to identical co-twins of patients was about 40 per cent., but there is evidence that the genetic factors underlying the condition are multiple, one group perhaps affecting the shape of the acetabulum, another the ligaments round the joint. One environmental factor acting in combination in the first group is related to season of birth, since the incidence is highest in babies born in mid-winter. Empirical risks for subsequent children are about 1 in 40 with both parents normal and 1 in 10 where one parent was also affected.

CONCLUSIONS

It will often be useful for the medical practitioner to bear in mind that information on the risks of recurrence may be had through the genetic clinics. Not only may this be helpful in answering patients' questions about the risks of recurrence in later offspring, but it may help in early diagnosis and treatment. For example, pyloric stenosis is the most likely cause of vomiting in infancy among the children of women who have also had pyloric stenosis. Hirschsprung's disease (fig. 3) is the most likely cause of neonatal intestinal obstruction in a younger brother of a boy with Hirschsprung's disease.

In the near future when more is known of the environmental factors which also play a part in causing some of the more common malformations, the aim of the medical profession will be to protect the genetically predisposed from developing the malformation.

Figure 3 is reproduced by courtesy of Butterworths Medical Publications, from 'Clinical Genetics' by Arnold Sorsby.

HEREDITY AND MENTAL DISEASE

By VALERIE COWIE, M.D., D.P.M.

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THE observation that mental disorder runs in families has been made throughout the ages. Unfortunately it is an idea still surrounded by much ignorance and superstition. Even in the twentieth century false beliefs and lack of knowledge bring untold misery to relatives of the mentally afflicted. Misinterpretation of facts has led to terrible programmes of sterilization in Nazi Germany, and in other countries where the aims may have been more sincere but, nevertheless, misguided.

The study of psychiatric genetics is still in its early stages, but sufficient is known to allay many of the fears commonly held regarding the transmission of mental disorder, and to provide a sound basis for genetical counselling.

HISTORICAL BACKGROUND

The scientific study of the inheritance of mental disorder began by the recording of pedigrees containing affected individuals. This method was favoured in Germany, where large-scale family studies were made at the end of the nineteenth and beginning of the twentieth centuries. Rediscovery of the Mendelian laws in 1900 gave added impetus to the work. Observers then began to look for Mendelian patterns in the familial occurrence of mental disorder.

In 1902 the work of Garrod on inborn errors of metabolism marked the beginning of a new phase in genetics. The geneticist turned his mind to biochemical considerations which have led to great advances in general genetical theory and to an understanding of the relationship between genes and enzymes. These developments have been of vital importance in the study of the inheritance of mental disorder. Investigations into genetically determined metabolic disorders with mental dysfunction such as phenylketonuria show great promise in throwing light on other conditions, possibly schizophrenia, in which the faulty mechanisms, no doubt gene-controlled, are still obscure. This fundamentally biological and biochemical approach to psychiatric genetics has superseded the large-scale pedigree studies. Two other lines of investigation have played an important part in the study of the inheritance of mental disease during the past few decades. These have been investigations in population genetics, and twin studies.

Notable work in population genetics has been carried out in the Scandinavian countries. Amongst others, Böök of Sweden has made outstanding contributions. These studies have shown the distribution of genes responsible for certain conditions throughout various populations, and the associated effects. They have given new insight into the inheritance of neurological and mental diseases.

Twin studies attempt to separate the effects of heredity and environment. They are based upon the belief that uniovular twins have identical genetical endowment, and that any differences, including the appearance of mental disorder in one of them, are due to environmental effect. Therefore a high rate of similarity among pairs of uniovular twins for a specific trait would indicate a hereditary factor. Binovular twins, however, follow the rule for ordinary sibs as regards genetical endowment. Kallmann (1950, 1953), in the United States, and Slater and Shields in Britain, have carried out twin studies on a large scale from the point of view of psychiatric disorder, and their findings are important in this field.

PRACTICAL APPLICATIONS OF PSYCHIATRIC GENETICS

The study of the inheritance of mental disorder in the various fields already outlined may seem at first glance to be of academic interest only. This is far from the truth. Genetical investigations often play a part in solving nosological problems: clear-cut disease entities emerge from a tangled mass of observations, and diagnosis and effective treatment may be made possible for the first time.

An even more direct practical application of this knowledge in medical practice is the basis it provides for genetical counselling. This is perhaps its most important aspect to the general practitioner who is approached for the kind of advice that may profoundly influence the lives of his patients and their relatives. In genetical counselling it must be borne in mind and explained at the outset that advice can only be given in terms of probability. From scientific study we are able to give an estimation of the approximate risk of affected children being born to parents who are themselves or who have close relatives afflicted with a mental disorder. These estimated risks are merely chances: no-one can promise with certainty that a given proportion of the progeny will be affected by, or spared from, the disorder in question. The advice is intended to give a picture of what the state of affairs is most likely to be, so that with this information the two partners can make up their minds themselves regarding marriage and childbearing, or decisions can be made regarding the adoption of children of parents with mental disorder.

With this as the aim and limits of genetical counselling, the order or risks attaching to various kinds of mental disorder will be briefly considered. It is quite beyond the scope of this article to give anything but a mere outline of our present knowledge of genetics in relation to the main specific types of mental disorder, but it is hoped that the following paragraphs will give some idea of the extent of doubt and certainty in the light of modern research.

AFFECTIVE DISORDERS

Extreme variations of mood, either in the direction of depression or of mania, and sometimes swinging from one to the other, are seen in the manic-depressive psychoses. Less extreme changes of mood are seen in the person

of cyclothymic temperament. They are seldom so severe that hospital treatment is called for, but they can be incapacitating. There is much evidence to support the belief that manic-depressive psychosis and cyclothymic temperament are determined by the same gene. Often an excess of cyclothymic individuals is seen in the families of manic-depressives. The basic personality of a manic-depressive is often markedly cyclothymic. Both manic-depressives and cyclothymic persons tend to be of pyknic body-build, indicating an underlying genetical constitution.

The theory advanced by Slater (1936), although not proved conclusively, fits many of the facts, and is today widely accepted: The manic-depressive psychosis is determined by a single autosomal dominant gene of weak and variable expression. Assuming this to be the case, approximately half the children may be expected to receive the gene where one parent is affected, as it is dominant. Sons and daughters are likely to be affected in roughly equal numbers, and the gene can be transmitted from an affected parent of either sex as it is autosomal and not sex-linked. Because it is considered to be of weak and variable expression, some of the gene-receiving children would be expected to be liable to manic-depressive psychosis in its form of full manifestation; in others the gene would exert a less marked influence and these children might have cyclothymic personalities; and in some cases the effect of the gene might be so weak as to have no noticeable consequences.

Slater has found the incidence of manic-depressive psychosis in the children of manic depressives to be 12.8 per cent.; this is in close agreement with Stenstedt's figure of approximately 12 per cent. (Stenstedt, 1952). Although these values indicate a relatively low incidence of manic-depressive psychosis in the offspring of affected parents, it should be understood that the figures do not include the cyclothymic temperament.

There is much discussion as to the possible heterogeneity of manic-depressive psychosis. For instance, psychiatrists are now inclined to believe that the non-phasic non-recurrent depressions of the involutional period belong to the category of manic-depressive psychosis, and the diagnosis of involutional melancholia is being made less often. On the other hand, genetical evidence suggests that they are separate entities. Much research is needed before the question of the subclassification of affective psychosis is settled, and genetical investigations are expected to play a large part in this.

The other major group of affective disorders are the neurotic depressions. They arise in individuals of neurotic temperament, often in response to some stress in the environment, hence the diagnosis of reactive depression. The evidence is against heredity playing any strong or direct role in the etiology of these illnesses, apart from its effect in producing the kinds of personality in which such depressions are liable to occur.

SCHIZOPHRENIA

There is a vast body of evidence to support the view that schizophrenia is a group of diseases sharing cardinal psychological symptoms and usually cul-

minating in the disintegration of the personality. No single genetical theory has been put forward to fit even most of the facts; the nearest approach to this has been the monogenic theory of schizophrenia put forward by Slater (1958), in which he proposes a single partially dominant gene as the genetical basis. Many genetical hypotheses have been made; some investigators, such as Kallmann, hold the view strongly that schizophrenia is determined by a recessive mode of inheritance, others are equally in favour of dominance. It seems extremely likely that schizophrenia will prove genetically heterogeneous, and in this way many of the diverse findings and hypotheses will fall into place.

One fact clearly emerges, however: it has been established beyond doubt that hereditary factors play an extremely important part in the etiology of schizophrenia. The present information regarding the incidence of schizophrenia in the offspring of schizophrenics is meagre. Kallmann estimates the incidence of schizophrenics among the children when one parent is schizophrenic as 16 per cent. and when both parents are schizophrenic as 68 per cent. Elsässer (1952) estimates the risk of schizophrenia in the children of two schizophrenics as 39 per cent.

EPILEPSY

Everyone is potentially epileptic. The threshold of stimulation required to produce an epileptic discharge shows individual variation. Indeed, even in the presence of an exogenous factor such as brain tumour, the tendency to fits may vary widely from subject to subject. Therefore the concept of epilepsy as a disease, divided for convenience into idiopathic and symptomatic types, is somewhat artificial. It is perhaps best from a genetical point of view to consider epileptic subjects as a group at one extreme of a scale of normal variation without arbitrary distinction and subdivision. Alström (1950) favoured this view, and divided his cases into groups whose etiology was unknown, probably known, and known. In these groups, the incidence of epilepsy among the children was 4, 5.4 and 3.2 per cent. respectively. These figures are of the same order as those of many other workers, who have found the incidence of epilepsy in the children, sibs and parents of epileptics as being between 3 and 6 per cent.

The importance of heredity as an etiological factor in epilepsy is upheld by strongly supportive evidence from twin studies. A most noteworthy investigation was carried out by Conrad (1937), who examined the cases of twins in the total number of epileptics in institutions in Germany. He found an extremely high incidence of epilepsy occurring in both twins of uniovular pairs, the figure being 67 per cent., and rising to 86 per cent. when only idiopathic epileptics were considered. The influence of heredity in epilepsy is further supported by electroencephalographic studies. Important investigations along these lines have been carried out in the United States by Lennox, Gibbs and Gibbs (1939, 1940, 1945), who found electroencephalographic abnormalities in a high proportion of parents of epileptics, and extremely similar records in epileptic uniovular twin pairs.

MENTAL DEFECT

The distribution of intelligence in the community may be compared with that of physical stature. In both cases, the measurements for the bulk of the population cluster around the mean value, and there is a falling away in number towards either extreme of the range, so that the well-known bell-shaped curve of normal distribution is produced. Heredity plays a large part in one's placing on this scale, either for stature or for intelligence, and one's position is determined in most cases by the combined action of many genes, each playing a small part. This is the rule for the inheritance of characteristics that show continuous variation, or small gradations between one individual and the next.

The majority of mental defectives can be thought of as being of below average mental stature, making up the lower end of the curve of distribution of intelligence in the community as a whole. Thus, their mental deficiency can be regarded as due to biological variation and the action by chance of many non-pathological genes. Mental defect due to this mechanism is essentially of clinically non-specific type. At the extreme lower end of the scale, however, there is too large a number of profound idiots to be accounted for by the effects of normal variation alone. This is due to the effect of single rare recessive genes producing severe specific forms of mental defect, such as phenylketonuria. In such cases the risk of parents producing more affected children after the birth of a mentally defective child can be estimated.

The wholesale sterilization of defectives is a deplorable measure which is in any case ineffective in reducing the number of cases in the community. Higher grade defectives do not necessarily produce children of as low a level of intelligence as themselves, and the great majority of patients of every grade of mental deficiency are born to parents who would not rank as mentally defective. In those cases of extreme mental deficiency of the most easily recognizable clinical types due to the action of pathological genes, the patient is infertile even if he lives to a reproductive age. All of us are the carriers of recessive genes capable of producing morbid conditions in a mating with a carrier of the same genes. It is from the pool in the general population that such genes are drawn, and in any marriage there is a chance that two gene-carriers are coming together. The chances of this happening are, of course, increased in cousin-marriage and in other types of inbreeding where, in the children, identical deleterious genes derived from a common ancestor may be brought together. It is in this fortuitous way that low-grade mental defectives are continually being born, and against this, eugenic measures such as the sterilization of mental defectives themselves are of no avail. The view is sometimes held, however, that sterilization may have a place in cases of social inadequacy, e.g. when, on account of his mental defect, the individual concerned would be unable to make the necessary provisions for bringing up a family. Every case, however, should be considered individually and with care.

MONGOLISM

It is impossible within the scope of this article to enter fully into a discussion of mongolism, but this is a clinical type to which special reference should be made, as the parents of mongols often seek advice about further childbearing.

In the past there has been much speculation regarding the etiology of mongolism. From a large body of evidence there have been points for and against a hereditary mechanism, and in recent years more and more evidence has accumulated suggestive of a genetical factor, although no conclusive decision could be reached. It was suggested by Penrose (1951) that constitutional susceptibility of the fœtus to mongolism could be due to a single very common gene, but that its manifestation would be largely controlled by factors connected with maternal age, which was apparently a very important factor in the etiology of the condition. Evidence strongly in favour of a genetical element in the etiology of mongolism included the familial occurrence of the condition itself, and the presence of signs which could be abortive forms of mongolism in otherwise unaffected close relatives of mongols.

A new light, however, has now been shed on the problem by recent findings of fundamental importance made possible by newly developed cytological techniques. In addition to the diploid number of forty-six chromosomes normally present in human material, a small extra chromosome has been discovered in cells from cases of mongolism (Lejeune *et al.*, 1959; Ford *et al.*, 1959).

Although their estimation is empirical and has been criticized as being of doubtful value, Böök and Reed (1950) have calculated that a woman who has already borne a mongol child runs the risk of about 1 in 25 of having another child similarly affected, and that the younger the woman is in the next pregnancy the better the prognosis.

PSYCHOPATHIC PERSONALITY AND NEUROSIS

Space is not available to discuss the possible hereditary factors in the less clearly defined diagnostic groups of psychopathic personality and neurotic states. It must suffice to say that these are essentially constitutional, and constitutional characteristics are produced mainly by the additive effect of many genes, each exerting a small influence.

PRESENILE DEMENTIA

Presenile dementia is a category in which genetics has played an important part in differentiating various conditions which have been perhaps too conveniently embraced by the single term. These conditions are clear-cut entities, distinct from one another not only in their pathology and clinical manifestations, but in their modes of hereditary transmission. Thus, for instance, there is evidence that Alzheimer's disease is determined by multifactorial inheritance, and Pick's disease is transmitted by a single dominant

gene. Huntington's chorea is also due to a single dominant gene. Studies of pedigrees containing it have shown that the manifestation rate is so high that nearly every person possessing the gene will develop the condition if he lives long enough. An affected individual can be expected to pass the gene on to approximately half of his children as it is a Mendelian dominant.

The dominant genes that arise by mutation and produce morbid conditions are often doomed to extinction because the individuals bearing them are rendered infertile by the conditions themselves. This, unfortunately, does not usually hold good for the presenile dementias. Thus, in Huntington's chorea the mean age of onset is about thirty-five years, by which time an affected individual will probably have had children, half of whom may be expected to possess the gene, and who in turn are likely to produce families and transmit the disease before they themselves show its signs.

CONCLUSION

In conclusion it should be emphasized that when advice is sought on a specific problem connected with the inheritance of mental disease, it is best to turn to the expert. Not only is a knowledge of genetics required but a practised psychiatric assessment of the situation is of the greatest importance. Accurate diagnosis must be ensured and questions of prognosis and social implications be taken into account. The whole matter must be approached with skill and care. The happiness, well-being, and even the existence, of many may depend upon the advice that is given.

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BLOOD GROUPS AND HEREDITY

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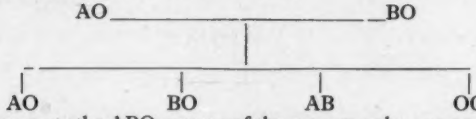
THE characteristics of human blood now known to show normal variants are very numerous. They include not only variants due to the antigens on the red cells, but those determined by antigens on the white cells and platelets, by the chemical varieties of hæmoglobin, of the β-globulins and serum characteristics known as Gm groups. It is proposed to discuss here only the 'classical' red cell groups: i.e. antigenic differences in the red cells of animals of the same species, as they are manifest in man. The blood groups of a person are genetically determined; they are present at birth though they may not be fully manifest then and, as they remain essentially unchanged throughout life, they are exceedingly valuable as genetic markers.

DISCOVERY OF THE ABO SYSTEM

The first blood-group system in man was discovered in 1900 by Landsteiner who described the occurrence of antigens A and B, either or neither of which may be present on the red cells of a given individual, thus defining groups A, B and O. He also made the fundamental discovery that the serum of a person contains antibodies to those of the A or B antigens which he himself lacks. Two years later his pupils, Decastello and Sturli, described persons who lacked both anti-A and anti-B; unfortunately they did not test the red cells and called the group 'ohne Gruppe', but this appears to be the first account of group AB. Soon after, Lewisohn reported a non-toxic anticoagulant, sodium citrate, which could be used intravenously in humans; this, coupled with the then purely academic discovery of blood groups, made blood transfusion, and indeed much subsequent work in this field, possible. (The clinical importance of the ABO groups had not been appreciated by the discoverers; it was others who realized that these antibodies might explain why many transfusions in the past had been unsuccessful, and who worked out the need for transfusing only ABO compatible blood.)

It was apparent fairly early that the blood-group antigens were inherited, but it was not until 1924 that their precise mode of inheritence was described by Bernstein. The existence of A and B genes had already been postulated; Bernstein introduced the idea of an O gene, carrying neither A nor B properties. He postulated that each person inherits one of the three genes A, B or O, from each parent (and thus has, according to Mendelian theory, two ABO genes).

If one parent has the genes A and O, and the other has the genes B and O, the children may be AO, BO, AB, or OO.



In this case, if one tests the ABO groups of the parents only, one can determine only that they are A and B respectively (i.e. the phenotype), but cannot tell whether they are AO or AA, BO or BB (i.e. the true genotype), because no antiserum corresponding to a specific product of the O gene is known. On testing all the family, however, it is immediately apparent that the parents must be of genotypes AO and BO, for a parent of genotype AA has no O gene to hand on and cannot therefore have a child of phenotypes B or O. Similarly, a BB individual cannot have a child of phenotype A or O.

Bernstein's theory has now been confirmed by the study of many thousands of families.

DISCOVERY OF THE MN GROUPS

The discovery of the ABO groups was facilitated by the fact that the antibodies anti-A and anti-B occur naturally, but in a search for further human blood-group systems Landsteiner and Levine (1927a, b) used a deliberate experimental approach. Rabbits were immunized by injection of human red cells and, with antisera so prepared, two further blood-group antigens, M and N, were demonstrated; it was subsequently shown that these were the product of allelic genes and were inherited quite independently of the ABO system. In the same year Landsteiner and Levine (1927b) described a further separate system, P, discovered by the same immunological methods.

In the MN system, as in the ABO system, an individual inherits one gene from each parent, but in this case there is no commonly occurring third gene corresponding to O. People may be MM, NN or MN, and the inheritance appears in the main to be quite straightforward. The MN system is of little or no clinical importance as anti-M and anti-N, which might for example cause transfusion reactions, occur but rarely in human beings. Certain antibodies, however, are occasionally found in human sera which define a further pair of alleles, S and s, closely linked to M and N. These are of great interest to blood-group geneticists, who are thus able to define four genes at this locus instead of the classical two, each person having two of the four gene combinations MS, Ms, NS or Ns. Unlike anti-M and anti-N attempts to prepare anti-S and anti-s in animals have so far been unsuccessful.

DISCOVERY OF THE RH SYSTEM

The most exciting and clinically the most important advance in blood groups since the original discovery of the ABO groups was, of course, the discovery of the Rh factor in 1940. This was made by Landsteiner and Wiener, also as a result of injecting red cells into rabbits—this time the cells of the rhesus monkey, *Macaca mulatta*. They showed that the resulting rabbit antiserum classified people into two groups according to the reactions of their red cells, those agglutinated by the serum being known as Rhesus positive and the others as Rhesus negative. This might well have remained an interesting

theoretical discovery, had not Wiener and Peters (1940) found an antibody giving identical reactions in the serum of a patient who had had a transfusion reaction.

Shortly before this, Levine and Stetson (1939) had demonstrated an antibody in the serum of a woman who had had a still-born child. The antibody

System	Positive reaction with specific antibody	Weak variants giving positive reactions with some antibodies, negative with others	Approximate phenotype frequencies in British Isles
ABO	**A_1 B. H**	A_2; A_3; Ax	A (A_1 + A_2) 42% B 8.5% O 46.5% AB (A_1B + A_2B) 3%
MNSs	**M.N.S.s** M^a; V^w; Hu; He; M^g; Vr	M_2; N_3; M^c	M 28% S + 55% MN 50% S — 45% N 22%
P_1	**P_1**; p^k	P_2	P_1 + 79% P_1 — 21%
Rh	**D**; **C**; **C**; C^w; C^x; **E**; **e**; E^w; **f**; **V**.	D^u; C^u; c^v; E^u	D + (Rh +) 82.5% D — (Rh —) 17.5%
Lutheran	**Lu^a**: **Lu^b**		Lu^a + 7.5% Lu^a — 92.5%
Kell	**K**; **k**; Kp^a		K + 7% K — 93%
Lewis	**Le^a**; **Le^b**		Le (a + b —) 22% Le (a — b +) 72% Le (a — b —) 6%
Duffy	**Fy^a**; **Fy^b**		Fy^a + 65.5% Fy^b + 83%
Kidd	**Jk^a**; **Jk^b**		Jk^a + 78% Jk^b + 73%
Diego	Di^a		O (see text)
Sutter	Js^a		O (see text)
Private	Levay, Becker, Ven, Wr^a, Be^a, Rm, By.		each <1%
Public	**Vel.** Yt^a **I**		each >99%

TABLE I.—The main blood-group systems.

agglutinated the cells of the woman's husband although they were both group O. Levine and Stetson suggested that the woman had been immunized against her husband's cells by the fœtus who had inherited the antigen from him. Subsequently it was found that this antibody was identical in specificity with the rabbit anti-rhesus antibody, and when Levine, Katzin and Burnham (1941) showed that it was the cause of hæmolytic disease of the newborn, the clinical importance of the new Rh group was then apparent.

FURTHER BLOOD-GROUP SYSTEMS

These discoveries led to an intensive search for antibodies in transfusion reactions and in cases of hæmolytic disease of the newborn. It was soon clear that in many cases antibodies could not be demonstrated in simple saline suspensions, as could the antibodies of the ABO and MN systems and new techniques had to be evolved. The elaboration of these techniques brought to light several new blood-group systems as well as alleles in the Rh system. Many puzzling anomalies from earlier days were explained—and many more puzzles were found for elucidation.

Originally the 'Rh-negative allele' was regarded as a 'silent allele', like O in the ABO system. Rh-negative red cells, in fact, invariably carry a number of antigens which are potentially dangerous—the silent d gene (q.v.) is usually accompanied by two others now known as c and e, which are both 'dominant' in that, given suitable antisera, each is recognizable in the heterozygous state. In a given population, such as that of this country, most blood-group antigens have frequencies between 5 and 95 per cent. In some systems, however, the main antigen is so common that only a very few people lack it, and in others so rare that the antigen is apparently confined to members of one or two families only; these groups are generally referred to as 'public', and 'private' or 'family', antigens.

The main blood-group systems are listed in table I.

The frequencies in table I are approximate phenotype frequencies only, and not gene frequencies; the very rare antigens are in lighter type. The table has been made exhaustive in order to indicate the variety of blood-group systems and the relative antigen frequencies in the British Islands. Most of these systems will not be further discussed. It should be mentioned here that many people (in England about 76 per cent.) secrete antigens corresponding to their ABO blood groups in water-soluble form in their saliva and other body fluids: this character is controlled by genes independent of those determining the ABO blood groups themselves. Secretor status bears a complex relationship, not yet fully understood, to the presence of the Lewis antigens on the red cells and in the saliva.

DISTRIBUTION OF BLOOD GROUPS

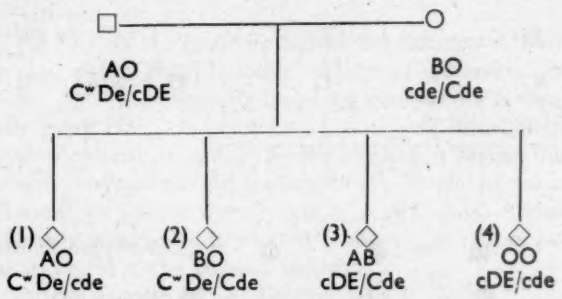
In general, the same blood groups are found throughout the world, but the relative frequency of these varies; for instance, to consider Europeans only, in Eastern Europe group B is very much more common than in Britain, the frequency rising as one goes East. In the area to the west of the Pyrenees, the Basque country, there is a high proportion of group O people and a lower proportion of group B than in the rest of Europe, and also the highest frequency of Rh-negative people in the world. In addition, a few blood-group antigens appear to be confined to certain races. One of these, Hunter (Hu), was described by Landsteiner *et al.* in 1934, and this, like Henshaw (He) (Ikin and Mourant, 1951), is linked with the MNSs system and is apparently found only in people of African origin. Similarly, the blood-

group antigen Sutter (Js^a), which appears to be independent of all other known systems, has so far been found only in people of African stock. The antigen Diego (Di^a) was first found in South American Indians in whom its frequency varies from tribe to tribe. It has since been shown to occur in North American Indians and Chinese and to be most common in Japanese, but has never been demonstrated in Caucasoids or Negroes. Studies of the distribution of these peculiar 'racial' antigens, as well as the frequencies of the common antigens, are important as throwing light on the ancient history of the peoples concerned.

LINKAGE

The term 'linkage' in a blood-group context should be used only in the strict genetical sense. Linkage is defined as the tendency for two or more pairs of allelomorphs to assort together at meiosis, because they are carried on the same pair of chromosomes. For the average geneticist this means that two genes are close together on the chromosome but not absolutely contiguous, so that in perhaps 10 per cent. of cases of meiosis they become separated. To the blood grouper, linkage tends to have a very special meaning, namely very close proximity such that separation at meiosis practically never occurs. This may be illustrated by the inheritance of the genes at the Rh locus.

The Rh system comprises at least three sets of allelic genes, C, D and E, with their respective alleles c, d and e. The number of possible gene combinations on a single chromosome is thus large, the commonest in Britain being CDe, cde, and cDE, with cDe, Cde and cdE less common. As each individual has any two of these triple combinations, it is apparent that the possible number of possible genotypes is enormous. If Rh groups are added to the family whose ABO groups are shown earlier the picture is as follows:—



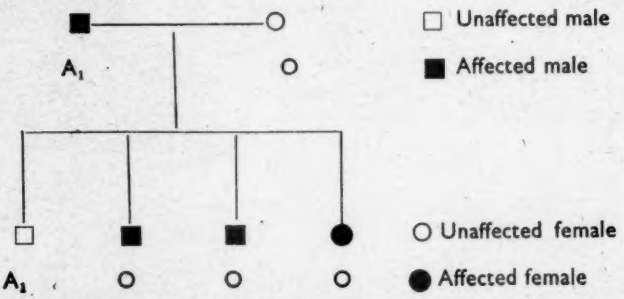
From this it is seen that the first child has inherited A from the father, and also his C^wDe. (C^w is a fairly rare allele of C and c; it has been chosen for this example so that it can be seen which children have inherited the father's $C^{(w)}$ gene.) The second child has also inherited his C^w and D, but not his A, though the third child has inherited his A, but not his C^w; this third child like the fourth who has his O, has inherited D and E. Similarly, both 2 and 3 have inherited B from their mother, but only 3 has her C.

This shows that the genes of the ABO system are inherited quite independently of the C^w and D genes, but the C^w and D genes are always inherited together. Extensive family studies show that, in fact, the three

Rh genes are inherited together: i.e. the four Rh gene combinations of this hypothetical pair are C^wDe; cDE, Cde and cde, the children who have inherited father's C^w, also have his e as well as D. More detailed studies of large numbers of families have confirmed the extreme closeness of the linkage between the three Rh loci. In this hypothetical family the children inherit either C^wDe from their father or cDE; the odds against a child having the father's C^w and E, and the parents thus having a child of genotype C^wDE/cde, are astronomical, for this postulates a cross-over, a phenomenon not yet observed between the genes of the Rh system.

Linkage has long been known in man, since the genes for some abnormalities are carried on the X sex chromosome, and so are linked to sex and to one another. Unfortunately no blood-group system is sex linked. Until recently no case of ordinary 'loose' linkage had been found on any of the other 22 chromosome pairs of man but, since everyone has demonstrable genes for numerous blood-group systems, the blood groups were clearly potential candidates for studies of linkage with congenital abnormalities as well as with one another. The first example of such a linkage was found by Mohr (1951) between the Lutheran blood groups and the ability to secrete the ABO antigens. The second example was that of Chalmers and Lawler (1953) between elliptocytosis and the rhesus locus. Shortly after, Renwick and Lawler (1955) published an account of another pathological condition linked with a blood group—the nail-patella syndrome (abnormalities of nails and absent patellæ) and the ABO locus.

This does *not* mean that all individuals showing this have the same ABO phenotype, or that all people of that group have the disease, but that in any one family the gene manifesting itself by this syndrome travels with one ABO gene, apart from occasional cross-overs.



This is a tiny part of a large pedigree of a family some of whose members have the nail-patella syndrome. It shows that the child who has inherited the father's A_1 group has not inherited his deformity, but those who have inherited his O group have inherited the defect. Such a tiny part of the tree would not constitute conclusive evidence of such linkage; far more extensive blood-grouping tests were done on 50 members of this family, as well as on many other families, and subtle and complex mathematical calculations were required to reveal the true relationship.

Linkages between blood-group systems and other conditions are now being sought and some results are promising; notably Lees *et al.* (1957) have

shown that anonychia, which is not an allele of the nail-patella syndrome, is probably linked with the Lutheran blood-group locus.

HÆMOLYTIC DISEASE OF THE NEWBORN

There are other diseases associated with blood groups that are not linked with them in the genetical sense. The best known of these, of course, is hæmolytic disease of the newborn. Icterus gravis neonatorum is no new disease.

> In 1729, George Cheseldon, wrote to Hans Sloane asking for advice for a patient who 'has had the misfortune to lose three fine boys who came into the world with very healthful symptoms for the first two days, and then the strongest signs of an icterus appeared the epidermis being all over tinctured alike which bad symptoms proved most certainly mortal in a few days, medicine being of no service to the infants'.

Many individual cases are described earlier than this in 17th century literature.

The discovery of the Rh factor provided an explanation for most cases of this disease which had been a mystery for so long. It was shown that a few red cells enter the maternal circulation and if they carry antigens which the mother does not possess, her system responds by making antibodies against these 'foreign' red cells; these maternal antibodies enter the fœtal circulation by an unknown route (possibly directly across the placenta, possibly via the liquor amnii) and destroy the fœtal red cells. The child may become gravely or mortally ill either from anæmia, or from the bilirubin resulting from the hæmolytic process, which cannot be adequately dealt with by the immature fœtal liver. For a long time it was thought that fœtal cells never entered the maternal circulation, but newer and subtle techniques show that, in fact, this happens quite often.

When the etiology of hæmolytic disease was first realized there was undue apprehension about 'the Rh factor'. Maternal immunization can in fact occur if the child possesses any blood antigen lacking in the mother, and practically every child has several such antigens, although the D antigen and the development of anti-D by the mother, is by far the commonest cause of severe disease. ABO incompatibility is also a common cause of immunization but disease due to this is usually mild. Almost all the Rh antigens in table I have led to hæmolytic disease, as well as anti-Kell, S; s; Fy^a; Di^a and most of the 'private' systems.

PROTECTION AGAINST IMMUNIZATION BY FŒTAL CELLS

Although no method is yet known for preventing spontaneous immunization of the mother by the fœtus, care and restraint in the transfusing of young women (to avoid 'artificial' immunization) and prompt treatment of affected infants has greatly reduced both the mortality and morbidity figures of this disease in the past ten years. As prompt treatment depends partly upon anticipating an affected baby the importance of adequate antenatal blood-group testing cannot be sufficiently stressed. On the other hand,

there is no need to cause needless anxiety to any mother because of her blood group. It is often overlooked how often Rh-negative women bear a series of healthy Rh-positive children without becoming immunized. It does not seem that the incidence of the disease can be higher than one in ten of pregnancies that provide the necessary Rh conditions and some authorities put the incidence much lower than that. It appears that there must be some mechanism of protection against immunization by the fœtus and subsequent hæmolytic disease in the newborn.

In the first place, it has been shown that a woman is less likely to be immunized by an ABO incompatible child (i.e. one from whom she could not receive a transfusion because of ABO incompatibility) than from an ABO compatible one. This may be because the naturally occurring antibody destroys the invading (fœtal) cells as soon as they enter the maternal circulation, and before they can provoke Rh sensitization. Once sensitization has occurred the ABO heterospecificity appears no longer to exert this protective effect. It appears that the protective effect of ABO incompatibility also applies when the mother (Kell-negative) is at risk to sensitization from a Kell-positive fœtus (Levine 1958). Other factors may also play a part. Murray (1957) showed that not all chromosomes carrying D are equally likely to cause hæmolytic disease, children who are cDE/cde being more prone to this, and also to be more severely affected than those who are CDe/cde.

Even these facts, however, do not explain fully why some women are more prone to sensitization than others. Animal experiments have shown that in certain circumstances a mature individual cannot make antibodies to an antigen to which it was exposed sufficiently early in its own fœtal development. From this it might be supposed that Rh-negative women with Rh-positive mothers would be less likely to make anti-Rh than those with Rh-negative mothers, since they had been exposed to Rh-positive stimuli *in utero*. Various studies showed, disappointingly, that this did not hold true directly; independent studies in England, New South Wales and California showed no disturbance of the Rh groups of maternal grandmothers of children with hæmolytic disease, compared with the normal population. The Californian workers, however, found that on counting only those Rh-negative mothers who had had three or more Rh-positive children, there were significantly more Rh-negative grandmothers in the group in which the mothers had antibodies than in the group who did not. It appears that this protection acquired *in utero*, which is called immune tolerance, is not the explanation of why some mothers develop antibodies, but it probably plays some part.

STATISTICAL ASSOCIATIONS OF BLOOD GROUPS WITH OTHER DISEASES

So far only diseases genetically linked with a blood-group system or caused by the direct immunological effects of the antigen have been considered.

There is, however, a further type of relationship between blood groups and disease, which has recently been the subject of much fruitful research: namely, the relative susceptibility of people of different blood groups to certain diseases.

The idea that there might be differences in susceptibility is no new one. Even before the precise mode of inheritance of the ABO groups had been worked out, Buchanan and Higley (1921) reported blood-group frequencies of 292 cases of carcinoma, 457 cases of pernicious anæmia and small numbers of cases of other diseases. The conclusions reached are worth quoting as an admirable summary of the nature of the problem.

'(1) We have shown no relationship between blood groups and any disease, *in which sufficient data are available to justify a conclusion.*

(2) The percentages of blood groups presented by Moss are approximate and capable of considerable variation without special significance.

(3) Nationalities should be taken into consideration in the presentation of statistical studies in blood grouping.'

In the thirty-five years following this tens, if not hundreds, of millions of blood-grouping tests have been done: the results of some six million have actually been published. Fairly exact blood-group frequencies for most parts of the world and amazingly detailed figures for all parts of the British Isles are available. Figures for the frequencies of blood groups of people suffering from certain diseases have been collected in series numbering many thousands, and on statistical analyses definite associations between some diseases and particular blood groups have emerged. It is perhaps satisfying to note that, when analysed by modern statistical methods, the figures from which Buchanan and Higley were loth to draw any conclusion show significant trends in the same direction as those shown by larger recent series.

Following the discovery of the Rh factor and the possibility of maternal immunization, some of the first statistical investigations were concerned with possible effects of parental groups on fertility. The literature on this subject is extensive, but the complications are many, and few well-established conclusions have emerged. It appears, however, that there is an increased proportion of groups B or AB in women who have one or more abortions (Sjösted *et al.*, 1951). There also appear to be fewer A children than would be expected from A x O matings (though the anticipated number from O x A). A x B seems a less fertile mating: but by contrast B x A is more fertile.

Much of the recent work in the field of blood groups and disease began empirically. The first significant investigation of this kind was that of Aird *et al.* (1953) showing a relationship between cancer of the stomach and the ABO system. In a series of 3,632 cases, they found a higher proportion of blood group A and a lower proportion of blood group O in patients suffering from this disease than in the general population of the locality in which they lived. It was realized from the outset that owing to regional frequency variations, controls must be taken in each case from the same locality. In this instance, blood group O is commoner in the north of England than in

the south, but group A is commoner in the south. Carcinoma of the stomach, however, is commoner in the north, but in any one area it is commoner in A than in O people. Thus it appears that there is an inherited element related to the ABO blood group in susceptibility to (or protection from) carcinoma of the stomach, but this inherited element is not directly related to the known geographical differences in the incidence of this disease.

As there had long appeared to be a connexion between carcinoma of the stomach and pernicious anæmia, it was of considerable interest when a similar significantly high frequency of A was found in cases of pernicious anæmia. At about the same time a raised incidence of group O in cases of peptic ulcer was found. Subsequent work separating gastric and duodenal ulcers has shown that, whilst the relationship in the case of the peptic ulcer is at best slight, duodenal ulcer gives the clearest picture yet found of association between a disease and a particular blood group.

It has further been shown (Peebles-Brown *et al.*, 1956) that the greater contribution to this group O excess was made by cases coming to operation. Moreover, those cases in which ulceration recurs after operation (stomal ulcers) have a particularly high frequency of group O (Wallace *et al.*, 1958). In duodenal ulcer, and possibly also in gastric ulcer, not only is there an excess of persons of group O, but also an excess of non-secretors of ABO blood-group substances—in the case of duodenal ulcer an excess proportionately even greater than that of group O. This relationship is found even within the family group when brothers and sisters with and without ulcers are compared. In the population as a whole, moreover, the relation between blood groups and ulceration is as marked among non-secretors as among secretors.

Many other diseases are or have been under investigation and strong but not overwhelming evidence has emerged in some cases for an association with a particular blood group. There can be little doubt of such an association of group A with diabetes mellitus and with carcinoma of the female genital tract.

DISCUSSION

The question arises: Why do we have blood groups? Do they perhaps have some protective value the nature of which is as yet barely perceptible? The blood-group antigens, which were originally regarded as the province of the immunologist only, are now being studied intensively by biochemists who have isolated substances which possess specific blood-group properties and are elucidating the chemical structures responsible for their serological specificity. Most of this work has been done on water-soluble blood-group substances the secretion of which, as previously mentioned, is under genetical control.

It has already been seen that most of the diseases which preferentially affect people of a particular blood group are diseases of some part of the digestive tract. Moreover, in at least one of them there is also a marked

association with non-secretion of blood-group substance. This raises the question whether the secreted substance may itself have an effect. The fact that for duodenal ulceration the relation between the blood groups themselves and the tendency to ulceration persists even in non-secretors shows that a direct effect of the secreted substance cannot be the whole story. Another hypothesis, that of a stratification of the population, with high O, high non-secretion and high tendency to ulceration in the one, and low values for all these quantities in the other, is disproved by the relation with secretion even within families, as well as by the relation of both duodenal ulceration and gastric carcinoma with blood groups in the populations of many countries and several continents.

It may nevertheless be anticipated that current investigations into the biochemistry of the blood groups themselves, and into the biochemical pathology of the diseases concerned, together with further critical statistical studies of the kind already described, may ultimately show the reason for the observed association and perhaps make some contribution to the prevention and treatment of the diseases themselves.

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CONSANGUINITY AND MARRIAGE

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CONSANGUINITY refers to the mating of genetically closely related individuals. In such marriages the chance that husband and wife will carry an identical gene, derived from a common ancestor, is considerably increased. Offspring resulting from a consanguineous marriage will therefore have a greater probability of receiving two identical genes. Since some hereditary diseases are due to the presence of the double dose of a specific mutant gene (homozygosity), such 'recessive' diseases occur with greater frequency among the offspring of consanguineous matings.

FREQUENCY OF CONSANGUINITY

The highest frequency of consanguinity is found in Japan—4.3 per cent. first-cousin marriages (Neel *et al.*, 1949). Both social custom and isolation of many villages evidently account for this high rate of inbreeding. First-cousin marriage rates for Denmark, France, Italy and Northern Ireland are somewhat less than 1 per cent. (Freire-Maia, 1957). In England, Wales, Germany and Holland, the frequency is probably lower than 0.5 per cent., whereas in the United States first-cousin marriages are very rare, being less than 0.05 per cent. (Freire-Maia, 1957). In some countries, such as Japan, Brazil, Switzerland, Northern Sweden, India and Israel, isolated areas or societies may be found where first-cousin marriages may reach 25 per cent. or more of the total number of marriages (Freire-Maia, 1957). In recent years, with better transportation and increased social mobility, cousin marriages have become increasingly rare in the western world.

GENETICS OF CONSANGUINITY

The basic genetic effect of consanguineous matings is to increase the number of individuals carrying the double dose of a recessive gene. Assume that a healthy subject carries a single dose (heterozygote) of a rare gene *a*, which in double dose (aa) produces clinical manifestations. Only a marriage with a person also carrying gene *a* would be of importance since one-quarter of the offspring of such a mating could inherit both abnormal genes (aa). First cousins share common grandparents; they are therefore much more likely to carry identical genes derived from a common ancestor than are unrelated individuals. Recessive diseases will thus be much more common among the children of cousin matings.

In table 1 are given the expected proportions of first-cousin matings for different frequencies of recessively inherited conditions and different fre-

quencies of consanguinity. The rarer the disease, the greater will be the proportion of cousin matings among parents of affected children (e.g. ichthyosis congenita—see table 2). This follows from the consideration that with increasing rarity of a gene, it becomes more and more unlikely that two

Frequency of condition	Frequency of first-cousin matings in the general population (per cent.)					
	0.05	0.10	0.50	1.00	2.00	5.00
1:1,000	0.1	0.3	1.4	2.8	5.6	13.2
1:10,000	0.4	0.7	3.5	6.8	12.8	27.4
1:100,000	1.0	2.0	9.3	17.1	29.5	51.9
1:1,000,000	3.1	6.0	24.2	39.0	56.4	77.0

TABLE 1.—Percentage of first-cousin parents among patients with recessive conditions.

unrelated marriage partners will carry the identical gene. On the other hand, there is a fixed, fairly high probability that relatives will receive an identical mutant gene derived from a common ancestor.

As consanguineous matings become rare in a population, the consan-

Disease	Percentage of first-cousin marriages among parents	Reference
Albinism	18—24	Neel *et al.*, 1949
Infantile amaurotic idiocy	27—53	Neel *et al.*, 1949
Juvenile amaurotic idiocy	15	Sjögren, 1931
Ichthyosis congenita	30—40	Neel *et al.*, 1949
Xeroderma pigmentosa	20—24	Neel *et al.*, 1949
Phenylketonuria	5—14	Penrose, 1954
Friedreich's ataxia	10	Penrose, 1954
Gargoylism	5	Halperin and Curtis, 1942
Deaf mutism	33	Furusho, 1957
Wilson's disease	38	Bearn, 1953
Congenital afibrinogenæmia	33	Hsia, 1959
Alkaptonuria	25—45	Harris, 1953
Cystinuria	15—25	Harris and Warren, 1953
Cystic fibrosis	0.4	Andersen and Hodges, 1946
Galactosæmia	9—24	Lowe *et al.*, 1949; de Grouchy, 1958
Total colour blindness	11—21	Neel *et al.*, 1949
Microcephaly	26	Van der Bosch, 1959
Adrenal hyperplasia	2	Childs *et al.*, 1956
Heredo-retinopathia congenitalis	16	Alström and Olson, 1957

TABLE 2.—Recessive diseases and consanguinity. The relative risk very roughly approximates the consanguinity percentage.

guinity effect in recessive diseases becomes less striking; e.g. a recent study of adrenal hyperplasia in the United States—see table 2. Table 1 also demonstrates that consanguineous marriages will be less frequent in common recessive diseases: e.g. cystic fibrosis—see table 2.

Consanguinity will have no effect on hereditary conditions inherited as dominants where a single gene dose causes full clinical expression. Since only one parent contributes such a gene to the affected child, it is of no consequence whether the parents are related. Mating between partners

carrying identical dominant genes is of genetic interest since some offspring may inherit the double dose of this gene, which may produce more severe disease or lead to early death (Allison and Blumberg, 1958). Marriages of this type will be more commonly encountered among related than among non-related individuals.

Sex-linked traits in males resemble dominant inheritance because only a single gene dose on the X-chromosome is required for clinical expression.

Fructosuria	Hypophosphatasia
Pentosuria	Fanconi's syndrome
Cerebral diplegia	Niemann-Pick disease
Porphyria erythropoietica	Fanconi's anæmia
Hageman trait	Gaucher's disease
Ac-globulin deficiency	Essential hyperlipæmia (severe variety)
Methæmoglobinæmia (enzymatic type)	Juvenile hæmochromatosis
SPCA deficiency	Pseudoxanthoma elasticum
Stuart Factor deficiency	Heredopathia atactica polyneuritiformis (Refsum's syndrome)
Hartnup disease	Retinitis pigmentosa (recessive variety)
Glycogen storage disease (all types)	
Familial cretinism	
Congenital nonhæmolytic jaundice with kernicterus	

TABLE 3.—Recessive diseases where one or several instances of consanguinity have been reported.

Consanguinity, however, would tend to increase the frequency of the exceptional female inheriting an X-chromosome with an identical mutant gene from each parent. Girls affected with a rare recessive sex-linked disease will therefore often be offspring of consanguineous matings.

Recent increased interest in consanguineous matings stems from the realization that such marriages provide information about the extent of

Author	Population	Control (per cent.)	First-cousin matings (per cent.)	Relative risk†
Schull	Japanese	1.02*	1.69*	1.6
Slatis	American	9.5	14.8	1.6
Böök	Northern Swedish	4.0	16.0	4.0
Sutter	French	10.9	28.0	2.6

*These figures only include congenital defects and omit various diseases and mental deficiency.

$$\text{†Relative risk} = \frac{\text{Percentage frequency in cousin matings}}{\text{Percentage frequency in control matings}}$$

TABLE 4.—Frequency (percentages) of all congenital defects and illness amongst offspring of control and first-cousin matings.

hidden recessive mutants in a population. Any intelligent evaluation of the genetic radiation risks requires this knowledge. Several authors have attempted to estimate the number of potential disease-producing recessive or lethal genes in the population (Slatis, 1954; Morton *et al.*, 1956; Penrose, 1957; Böök, 1957; Schull, 1958; Slatis *et al.*, 1958). The data agree that the average individual carries about one to two lethal and another one to three detrimental genes which could produce pathological effect in the homozygous

state. Böök (1957) also estimates from his data that the total number of recessive genes with recognizable major detrimental effect in homozygotes ranges between 150 and 450. The partial listing of at least 42 known recessive diseases (tables 2, 3) may be compared with this estimated figure.

EFFECT OF CONSANGUINITY ON SPECIFIC RECESSIVELY INHERITED DISEASES

Actual data have borne out that cousin marriages have led to an increase of recessively inherited diseases. Table 2 lists those diseases for which fairly

Defect	Relative risk*	Author
Most CNS malformations (e.g. hydrocephalus) including undefined neurological diseases	6	Sutter, 1958
Mental deficiency	6	Sutter, 1958 Böök, 1957 Penrose, 1954
Simple cleft palate	5	Schull, 1958
Some congenital cardiac defects (e.g. pulmonary stenosis, atrial septal defect)	3	Lamy *et al.*, 1957
Complex abnormalities	3	Schull, 1958
Atresia ani	4	Schull, 1958
Anophthalmos and/or microphthalmos	3	Schull, 1958
Oligodactyly	7	Schull, 1958
Many nonspecified malformations	?	

$$\text{*Relative risk} = \frac{\text{Percentage frequency in cousin matings}}{\text{Percentage frequency in control matings}}$$

TABLE 5.—Congenital defects shown to be increased amongst offspring of consanguineous matings.

extensive data are available, and gives the proportion of first-cousin matings among the parents. Table 3 lists other recessive diseases in which consanguinity has been demonstrated but where, due to lack of data, no quantitative estimates have been made.

The relative risk of a consanguineous mating refers to the chance of a consanguineous union producing an affected child compared with the probability of an affected child issuing from a random mating. Relative risk can be calculated by dividing percentage of abnormal children in cousin matings by percentage of abnormal children in random matings (see tables 3, 4, 5). The data necessary for an exact calculation of relative risks for rare recessive diseases are not available. In these instances the relative risk is approximated very roughly by the percentage of first cousin matings among parents of affected offspring (see table 2). Thus, a cousin mating is approximately 5 to 14 times more likely to produce a phenylketonuric child than a random mating since the consanguinity percentage in this disease ranges from 5 to 14 per cent. (table 2).

The absolute risk which refers to the actual probability of a child with consanguineous parents to be affected is still quite low. Assuming an average frequency of 1:40,000 for most of the diseases listed, the risk for a child of a first-cousin mating to be affected with a specific disease would be

1:3,200. The risk that a child from a consanguineous union will be affected with any one or more of the 42 conditions listed in tables 2 and 3 will be around 1 per cent. Since the actual number of recessive conditions is undoubtedly higher and the actual incidence of the various recessive genes varies considerably, the figure of 1 per cent. should not be taken literally but represents the order of magnitude of the risk.

EFFECT OF CONSANGUINITY ON CONGENITAL DEFECTS AND MENTAL DEFICIENCY

Various studies have shown that in addition to a marked increase in the incidence of specific rare recessive diseases amongst offspring of cousin marriages, such matings also lead to an increase in the incidence of some congenital malformations and of mental deficiency (Bemiss, 1858; Arner, 1908; Böök, 1957; Slatis *et al.*, 1958; Schull, 1958; Sutter, 1958). Some of these defects are known to have a genetic basis, whilst others are obscure in origin. The consanguinity effect in the latter instances obviously points to a genetic etiology. Although the effect of cousin matings on congenital defects is much smaller than that demonstrated for rare recessive diseases (compare table 2 with tables 4 and 5), the absolute or *actual* risk for the individual child with first-cousin parents is somewhat higher because of the generally greater frequency of these abnormalities.

Table 4 lists the total frequency of various defects and other illness in children of first-cousin marriages as compared with control populations. None of these investigations cited can be strictly compared with each other since the criteria for the diseases included varied considerably. It should *not* be concluded from this table that the incidence of congenital defects and disease in the populations studied is markedly different. Table 4 demonstrates that the risk of abnormal children issuing from consanguineous unions is approximately twice the risk for children of random matings. Table 5 lists specific malformations and their relative risks. This table was compiled by selecting only those defects which showed a marked consanguinity effect. The actual risk for mental subnormality may be higher than can be documented by objective data since one observer (Sutter, 1958) was impressed by mild intellectual impairment in children of consanguineous matings. It has also been reported that intelligence in the royal families of Europe decreased as such dynasties became increasingly inbred (Asdell, 1948).

The finding of a significant increase of complex anomalies involving multiple defects among children of consanguineous parents should be emphasized (Schull, 1958; Sutter, 1958). The etiology of such complex syndromes is not known. They may represent unrecognized recessive syndromes with multi-organ expression of a common basic recessive defect (pleiotropy). Sometimes, such complex anomalies may result from the rare, but increased, chance that a child from a consanguineous union may be homozygous for two independent recessive conditions. Another possible

explanation relates to the suggestion that normal development is under control of a system of many interacting heterozygous genes (Lerner, 1954). Development anomalies, according to this concept, could be caused by increased homozygosity for such genes. Consanguinity, by increasing homozygosity, would lead to interference with orderly normal development and thus tend to produce complex abnormalities rather than single specific defects. Neel (1958) concluded that his data on congenital defects would be compatible with this concept.

EFFECT OF CONSANGUINITY ON MORTALITY

The effect of consanguinity on mortality has been studied by several investigators. There is general agreement that there is little or no effect of consanguinity on prenatal mortality (Böök, 1957; Schull, 1958; Slatis *et al.*, 1958; Sutter, 1958). Thus, abortion and stillbirth rates are not significantly different from those observed in random matings. Similarly, fertility and sterility show no consistent deviations from control population values. These data therefore offer no evidence for the existence of rare recessive genes operating during early or late fœtal life. Although no increased sterility is observed in consanguineous mating, it would not be unreasonable to search for sterility among the *offspring* of such matings since homozygous recessive genes may lead to impaired fertility. Darlington (1958) cites five double marriages in which a man had children by two wives, one a cousin, the other an unrelated woman. The number of great-grandchildren derived from the cousin matings was significantly smaller than those of the random marriages. Further studies on this problem are required.

Table 6 summarizes the findings on postnatal mortality. There is general agreement that mortality is slightly but significantly increased amongst offspring of consanguineous matings. Sutter (1958) points out that the mortality in children of consanguineous mating is distributed over all age-groups from birth to 30 years with no mortality excess at any particular age. Thus, genetic lethality affects not only young children but is still operative during adulthood. Increased mortality in the offspring of consanguineous matings is probably due to homozygous recessive genes with subtle and, as yet, undetectable effects. It is likely that with the rapid advances in human biochemical genetics many of these obscure states will be diagnosed in the future. Mortality would then be clearly related to the effect of specific recessive syndromes rather than considered by itself.

PRACTICAL CONSIDERATIONS

Since consanguinity effects may be of great help in the identification of difficult diagnostic problems, such as recessive diseases, it is desirable to note this criterion in obtaining family histories. In eliciting a possible history of cousin marriage, it is helpful to note the patient's name, the mother's maiden name as well as both the paternal and maternal grandmother's maiden names. If any two of the possible four names are identical, it is not unlikely that a cousin marriage exists.

Cousin matings definitely increase the risk of rare recessive diseases, some congenital malformations, mental deficiency and postnatal mortality in offspring. The relative risk of a rare recessive syndrome is considerably increased over a random mating. Since such recessive diseases are un-

Author	Age range studied (years)	Mortality		Relative risk
		Control	First-cousin matings	
Bemiss, 1858	0—30	16.0	24.1	1.5
Arner, 1908	0—20	11.6	16.7	1.4
Sutter, 1958	0—30	12.3	22.0	1.8
Slatis, 1958	0—20+	2.4	8.1	3.4
Bŏŏk, 1957	0—30	14.0	21.6	1.5
Schull, 1958	0—8 (liveborn only—Hiroshima)	5.5	11.6	2.1

TABLE 6.—Effect of consanguinity on mortality (percentage).

common, the actual risk for children of a consanguineous marriage to be affected by any of these diseases listed in tables 2 and 3 is quite small—probably about 1 per cent. Significant congenital malformations are relatively frequent in the population (approximately 1 per cent.). If one considers all such malformations, the risk of a consanguineous offspring being affected is approximately twice that of a child from a random mating (table 6). For certain abnormalities such as those of the central nervous system (table 5), the risk becomes higher (6x). The relative risk of children of consanguineous matings being affected by mental deficiency and subnormality is considerably higher than normal. The absolute risk that a child of a first-cousin union may be mentally subnormal, however, remains small—probably about 3 per cent. as compared with 1 per cent. in the general population. There is increased postnatal mortality among children of first-cousin marriages. The relative mortality risk is probably less than twice that of offspring from random matings.

The presentation of risk figures for a consanguineous mating to potential cousin partners is not an easy task. Since the total actual risk of diseases or malformations is relatively small, some physicians might choose to emphasize the probability that such children will most likely be well and healthy. On the other hand, there already exists a significant amount of hereditary illness of various types in the population. Consanguinity increases the risk of some of these diseases. Since certain of these conditions represent a heavy personal, psychological, social, and financial load, potential consanguineous parents should be warned about the increased risks. Ultimately, the decision whether to marry a cousin should be left to the potential partners. It is comforting to know that the problem is becoming less important in most societies today since modern conditions allow the selection of a relatively wide range of non-related mating partners.

SUMMARY

Consanguinity increases the clinical expression of recessively inherited diseases by allowing two identical abnormal genes to become associated in the same individual.

Consanguinity effects have been demonstrated for a variety of rare inherited structural and metabolic abnormalities, some congenital defects, mental deficiency and postnatal mortality.

Consanguinity other than first-cousin marriages is of little practical importance.

The relative and absolute risks for the various diseases and abnormalities are reviewed.

Although the relative risk of consanguinity may be quite high for certain diseases, the absolute or actual risk of children to be affected with any hereditary pathological condition is much lower.

(Calculations for the unexplained quantitative statements in the text are given in an appendix furnished with the reprints of this article.)

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HEREDITY AND SEX-DETERMINATION

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Sex is the term used to describe the division of the individuals of a species into two complementary and more or less contrasted forms known respectively as male and female (the two sexes). The individuals of a species in which such sex-dimorphism exists produce two kinds of gametes, the spermatozoon and the ovum, these being distinguishable by differences in structure and behaviour. A male, essentially, is an individual equipped for the production of spermatozoa and for the conveyance of these to the site of fertilization. A female, essentially, is an individual equipped for the production of ova and for the conveyance of these to the site of fertilization. These are the key differences between male and female, but in many species others have been added to them. In the mammal, for example, the female, in contradistinction to the male, is equipped for the entertainment of the fertilized ovum and its derivatives, the embryo and fœtus, within her body, for the bringing forth of the offspring and for the postnatal nourishment and protection of the immature young. In our species, as in many others, the sexes are to be distinguished by reference to differences in (a) the chromosome complex present in the nuclei of the cells of which the body is composed, (b) the structure and endocrine function of the gonads and the anatomy of the rest of the internal genitalia, (c) the anatomy of the external genitalia and (d) the secondary sexual characters. These differences are biological in nature and are not affected to any discernible extent in their manifestation by influences emanating from the social environment in which the individual pursues its development.

X- AND Y-CHROMOSOMES

The chromosome number characteristic of *Homo sapiens* is 46. The chromosomes are present in the nucleus of the cell in the form of 23 pairs. Of these, 22 pairs (the autosomes) are common to both sexes but in respect of the remaining pair male and female differ. For this reason the members of this pair are called the sex-chromosomes. In the female the two members of the pair are alike. In the male one member of the pair is like the two members in the female. These three chromosomes are known as X-chromosomes. The mate of the X in the male is relatively small and is known as a Y-chromosome. In so far as the sex-chromosomes are concerned the male can be symbolized as an XY individual, the female as an XX individual.

'NUCLEAR SEX'

This difference can be observed in appropriately prepared microscopic slides but it is not easily detected, for the chromosomes are many and

minute. A simpler method has become available during the last decade. The so-called 'nuclear sex' of an individual, tissue or cell is identified. The stuff of which the chromosomes are compounded is nucleotide material (deoxyribonucleic acid; DNA). When this is prepared and stained in appropriate ways in microscopic sections, in oral mucosal smears or in cellular debris from the liquor amnii, for example, it is found that in material derived from the body of a female, as defined above, two minute masses of DNA, drum-stick-like in shape, can be recognized and that in material derived from the body of a male, as defined above, these masses are absent.

GENETIC SEX

It is established that into every ripe gamete produced by the individual there passes one member, it matters not which, of each and every pair of chromosomes. Every spermatozoon and every ovum produced by members of our species will have in its nucleus 22 single autosomes and one sex-chromosome. Since the female characteristically has two X-chromosomes, each and every ovum will include an X. The human female is constitutionally homogametic, producing only one kind of gamete in so far as the sex-chromosomes are concerned. The male, XY, is necessarily heterogametic and produces two kinds of spermatozoa, one carrying an X-chromosome and the other a Y. Fertilization, essentially, consists in the reconstruction of the chromosome complex characteristic of the species by the conjunction of two half-sets of chromosomes, one being contributed by each of the parents. An ovum fertilized by an X-chromosome-bearing spermatozoon will inevitably yield an XX individual, a female; the same or any other ovum fertilized by a Y-chromosome-bearing spermatozoon will yield a male, XY. The phenomenon of sex-linkage (see p. 137) provides evidence which demonstrates conclusively that these statements are beyond dispute.

The (genetic) sex of the individual is determined at the moment of conception by the spermatozoon, X- or Y-bearing, that happens to fertilize the ovum. Because the XY and the XX constitutions of the fertilized ovum so clearly seem to be causally related to the assumption of the male and of the female characterization respectively it is generally accepted that maleness and femaleness are genetic characters. There are male-determining and female-determining genes. In our species the former would seem to have become congregated in the autosomes, the latter in the X-chromosome. If A is taken to represent one half-set of autosomes, then male and female can be symbolized respectively as 1X:2A and 2X:2A. The balance between the two kinds of sex-determining genes differs in the two sexes. In the male, because he is 1X:2A, the male-determining forces are in effective excess during the time when the gonads are developing and for this reason they develop into testes. In the female, the female-determining forces are in effective excess at this time and so the gonads become ovaries.

THE ROLE OF THE HORMONES

From this point onwards the control of the processes that yield sex-dimorphism passes from the genes to the endocrine system as this develops. In every individual the sex-hormones, the sex-differentiating forces, are elaborated. In every individual, XY or XX, with testes or with ovaries, both male- and female-differentiating forces are present. In the individual with testes, however, the male-differentiating forces are in effective excess during the time when the rest of the internal genitalia, the external genitalia and the secondary sexual characters are developed. In the individual with ovaries, on the other hand, the female-differentiating forces are effectively in excess. For these reasons, in the individual with testes, the male-type characterization is assumed, in the individual with ovaries, the female-type.

This greatly condensed and simplified account has concerned itself with 'normality', i.e. with the usual. In it the two points of importance are (i) the matrix of the fertilized ovum and the soma of the developing embryo are ambivalent and (ii) the decision as to which of two alternative types of characterization shall be displayed is made by the balance that exists between two opposing forces. An appreciation of these points contributes considerably towards an understanding of a number of remarkable abnormalities and unusual occurrences.

SEX-REVERSAL

The balance between the male- and female-determining genes is ultimately determined by the relative number of autosomes and X-chromosomes. The distribution of the chromosomes during gametogenesis is not invariably in accordance with the rule. Maldistribution takes many forms; whole chromosomes can get left out of the nucleus; the members of a pair can fail to separate after conjugation. A nucleus can come to possess more or less than 46 chromosomes. The fertilized ovum can come to possess one single sex-chromosome or three, it can be XXY or XXX. All such happenings result in a greater or lesser disturbance of the 'normal' balance between the male- and the female-determining forces and can lead to the development of an inter-sexual condition and, it would seem, even to complete sex-reversal. Recently, evidence has been presented that suggests very strongly indeed that about one in every four hundred males (human) is in fact a completely masculinized female. The 'nuclear sex' is female but the sex accoutrement typically male. The cause of this sex transformation would seem to be an unusual numerical proportion in an XX individual of male- and female-determining genes due to the maldistribution of autosomal material (e.g. 2X:3A).

It is established that the administration of testosterone to a pregnant woman during the earliest stages of pregnancy in attempts to prevent spontaneous abortion can lead to the masculinization of a female child (XX). This procedure disturbs the balance between the male- and female-

differentiating forces operating within the embryo with the result that the male-differentiating forces come to be in effective excess.

Assume for a moment that sex-reversal, due to a disturbance of the balance between the sex-determining or of the sex-differentiating forces, is complete and that an XX individual does come to display the sex accoutrement of the male and to function as a male, what then is the true sex of the individual? It is to be noted that the sex-chromosome constitution of the individual cannot be accepted as an indication of the individual's sex. In many species it is the male who is XX in constitution and is homogametic, and the female who is XY. In certain fish both XY and XX males are encountered, the XX male being a completely transformed female, the sex-reversal occurring in the mature individual. Both kinds of male are functional. The definitions of maleness and femaleness must surely be applicable to all species in which these characters are encountered. The cock of the domestic fowl is no less a male than a ram, yet one is XX and the other XY. The usefulness of this XY-XX mechanism lies in the fact that it ensures that males and females shall be present among the offspring of the matings of males and females; one of the sexes must be heterogametic, it matters not which. It is to be assumed that in those species in which the male is XX the male-determining and not the female-determining genes have become congregated in the X. The only difference between the normal XY male and the XX male, the product of the process of sex-reversal, is that the latter, if fecund, can beget only daughters since he, like his mate, is homogametic.

INTER-SEX

It is established that partial masculinization in the human female can result from a disturbance of the male-/female-sex-hormone balance due to disease of a member of the endocrine system. In the sex accoutrement there are several characters that are common to the two sexes but which attain a greater degree of development in the male. For example, the clitoris is not as large as the penis and is capable of further growth; the distribution of hair differs in the two sexes but the female pattern can become replaced by the male if the controlling force changes. If the stimulus changes then all those structures of the sex-accoutrement that can respond will do so.

The inter-sexual condition is not infrequently encountered. Of it there are many grades. Some would seem to be instances of incomplete sex-reversal, others of a delay in the expression of the sex-differentiating forces. The sex accoutrement is not developed all at once: there is a time-seriation of events, the different components being developed and becoming differentiated at different times. If for any reason the gonads did not become differentiated at the proper time then by the simple process of growth and in the absence of any control the genitalia would develop. The uro-genital cleft and genital tubercle would get bigger to become well-grown editions of their embryonic

forms, the derivatives of both Müllerian and Wolffian ducts would grow so that the individual would come to possess a double set of internal genitalia. The extent of this undirected growth, the degree of this inter-sexuality, can serve as an indication of the extent of the delay in the expression of the controlling influence of the differentiated gonads. The sex of an inter-sex is indicated by the structure of the gonads. In the case of a hermaphrodite, with both testicular and ovarian tissue, the individual is indeed a composite of male and female. By the removal of one of the two forms of gonad the individual can be transformed, though probably imperfectly, into a male or else into a female.

This surgical correction of the consequences of a fateful indecision is entirely reasonable. It differs essentially from surgical intervention in instances of transvestism. Although the surgeon may bedeck a mutilated male with the anatomical habiliments of a female, this does not change the sex of the individual, whatever the law may have to say upon the matter, unless the transplanted ovarian tissue survives. If it does not, then the individual remains a mutilated male.

CONCLUSION

When discussing this phenomenon of sex-determination, it has to be remembered that sexual reproduction, made possible by the invention of sex, has played a most important role in our evolutionary history as a species. The genes in the chromosomes elaborate their products of a specific chemical nature and these control the processes of development. Genes mutate and the mutant gene exerts an influence more or less different from that of the gene it replaces. Mutation is the process that has provided that genetic variety which has been exposed to the appraisal of the selective forces in the environment. Evolution has resulted from the action of selection upon genetic mutant forms. Sexual reproduction has been the means whereby the evolutionary process has been greatly expedited. It has made it possible to obtain an accumulation of advantageous mutational steps without having the respective multiplications of these steps occur in series. Instead they have occurred in parallel with concomitant interpenetration and combination in the respective lines of descent. Advantageous mutations that have occurred separately in the two lines of descent of the parents have been brought together to act in an additive manner. It is because sex has conferred such advantage upon the species displaying it that it is so widespread.

TWINS AND HEREDITY

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Two aspects of twinning are relevant to genetics: first, the hereditary factor in the production of twins, and secondly the use of twin studies to widen our knowledge of human genetics. The frequency of twin births varies in different countries but averages about 1 per cent. of all births. The frequency of twin pregnancies must be greater than this for there is a higher than average rate of abortion in multiple pregnancies. It is generally accepted that there are two types of twins, monozygotic and dizygotic.

MONOZYGOTIC TWINS (MZ)

Monozygotic (uniovular, homologous, identical, similar) twins result from the cleavage of the fertilized ovum into two separate embryos. MZ twins therefore carry the same genes and are of the same sex. Rarely, the separation is incomplete, giving rise to so-called Siamese twins.

The twinning of the single fertilized egg may occur at any of three stages in its development:—

(1) Before the blastula is formed (2 to 4 days), in which case there will be two chorions, two amnions and two (although often fused) placentæ.

(2) At the blastocyst stage when the rapidly dividing cells produce the first clump of embryo-forming cells. The two embryos in such case have individual amnions but there is only one chorion and one placenta, which is the commonest occurrence.

(3) Rarely, at about the fifteenth day by the formation of two embryonic nodes instead of the usual one, in which case the twins share a common single chorio-amniotic chamber.

The rate or frequency of MZ twinning varies little from country to country and bears no relationship to increasing maternal age and parity. Further, MZ twinning does not 'run in the family'. In these three respects it differs from dizygotic twinning. In this country about 30 per cent. of twins are MZ. The cause of MZ twinning is probably the local presence of retarding factors such as delayed implantation or deficient supply of oxygen or nutrients. Biologists have produced MZ multiple births in animals, not only by mechanical separation of blastomeres but also by the use of physical and chemical agents.

DIZYGOTIC TWINS (DZ)

Dizygotic (binovular, heterologous, fraternal, dissimilar) twins result from the separate fertilization by two different sperms of two ova released from the same or, more often, different follicles at about the same time. They are no more alike in heredity and sex than any two children of the same parents.

Each twin has its own amnion, chorion and placenta but the two placentæ often fuse. Unlike MZ twinning, the DZ type is related to increasing maternal age and parity and to heredity. Consequently the rate varies in different countries and is also affected by the prevalence or absence of restriction of family size.

The hereditary factor in DZ twinning lies with the mother in that she inherits, and may transmit, the 'knack' of double ovulation. From time to time, however, evidence has been adduced purporting to show that there is a paternal hereditary factor in dizygotic pregnancies. The determination of the exact genetic basis is made difficult by the apparently low penetrance of the gene or genes, but for which the frequency of dissimilar twinning would presumably be much greater than it is. It may be that increasing maternal age and parity affect the penetrance of the relevant genes, perhaps by determining the intra-uterine survival of the pregnancy.

The multiple births of triplets, quadruplets and so on may be MZ or DZ or a combination of both. For example, the Dionne quintuplets were uniovular but the Argentine quintuplets were pentovular.

IS THERE A THIRD TYPE OF TWIN?

From time to time other modes of origin of twins have been suggested. The theory most often put forward is that both the ovum and the second polar body may be fertilized by separate sperms, or that the ovum may produce two daughter cells both of which may be separately fertilized. Such theories are aired in order to explain a pair of twins who are not identical, perhaps being of different sex, but who are more similar genetically than sibs. Such a theory is unnecessary, however, for chance alone can produce such genetic similarity, as indeed it may do in sibs born at separate times.

TWIN STUDIES IN HEREDITY

Galton, in 1857, was one of the first to recognize the value of the study of twins 'as a Criterion of the relative powers of Nature and Nurture'. But the scientific use of twin studies only became possible when MZ and DZ twins could be distinguished from each other. In 1924, Siemens introduced a polysymptomatic diagnostic method for this purpose; today we rely not only upon physical characteristics but also on the more precise study of blood factors, inherited serum proteins and fingerprint patterns. The 'take' of reciprocal skin grafts suffices in itself for the accurate diagnosis of MZ twins but, although this has been used as a conclusive test of identity in a few medico-legal cases, it is a rather drastic weapon to employ in genetic research.

The application of twin studies lies mainly in an attempt to assess the relative parts played by heredity and environment in the development of an individual and in his resistance and susceptibility to disease. Concordance for a particular character or condition has been the method most often used, a comparison being made of the relative proportions of MZ and DZ twin

pairs showing the condition under examination. This provides a simple first test for there being a genetic factor in that particular character or condition. Schemes of investigation include the following:—

(1) *Study of MZ twin pairs brought up together.*—Here the environment is the same, so that differences between the individuals of a pair should show the range of variation possible in the same genotypes. Such variation does occur, indicating that the penetrance of the same genes may vary in an MZ pair; for instance, one may be a 'taster' of phenylthiocarbamide (an inherited ability) and the other not. But even in the same home non-genetic agents may produce phenotypic differences despite identical genotypes. For instance, one twin may develop diabetes mellitus, to which there is a genetic predisposition, because of overeating whereas his more moderate twin may develop it much later or not at all. A further refinement in this group of studies would be to separate dichorionic from monochorionic MZ twins.

(2) *Study of MZ twin pairs who had been reared separately from an early age.*—Unfortunately, but not unexpectedly, such separated pairs are hard to find. Differences here should be due almost entirely to environment. Or, more accurately, the differences in this group, less the differences in the previous group, should show effects of environment only.

(3) *Study of DZ twin pairs brought up together.*—In the same environment all differences should be due to heredity. DZ twin pairs brought up separately from an early age can also be studied for comparison. In this group like-sexed pairs only are used so as to exclude the influence of sex itself.

(4) *Study of sib pairs as controls.*

(5) *Comparison of the similarities and the differences between the individual members of each pair in each group, and between pairs in different groups.*—For example, comparison of the range of differences between DZ pairs (due to both heredity and environment) with the range between MZ pairs brought up together (due to environment alone) gives some idea of the relative strength of nature and nurture in the differences in DZ pairs.

No. of pairs	Type	Mean intrapair difference (in months)
51	MZ twins	2.8
47	DZ twins	12.0
145	Sibs	12.9
120	Mother and daughter	18.4
120	Unrelated women	18.6

TABLE I.—Results of an inquiry into the relative importance of heredity and environment in determining the age of onset of menstruation. (After Petri, 1934.)

As a simple example, the results of an inquiry into the relative importance of heredity and environment in determining the age of first menstruation are shown in table I.

This table shows (a) the much smaller mean intrapair difference in MZ than in DZ twins; (b) the little difference between DZ twin pairs and sib pairs; (c) the greater effect of environmental differences in different generations of the same family than in the same generation.

Similar studies have been made in respect of many characters, physical (e.g. height, weight), physiological (e.g. blood pressure) and mental (e.g. intelligence). For instance, I.Q. scores in twins vary with environment but there is a greater similarity in the scores of MZ twins, whether raised together or apart, than in DZ twins brought up together. In general there is some, but surprisingly little, difference between the findings for the individuals of MZ twin pairs whether reared together or not. From these studies it was a natural step similarly to investigate diseases and even criminality. For example, in diabetes mellitus the incidence of concordance is 5 times as high in MZ as in DZ twins; when MZ twins both develop the disease it is nearly always in the same year, and often the severity of the disorder is similar. With regard to cancer, less illumination has been obtained as yet. If malignant disease, or cancer in a certain site or organ, is concentrated in certain families there should be an excess of concordant pairs in both MZ and DZ twins, and if the concentration is mainly genetic the excess should be much greater in MZ pairs. Most recently the smoking habits of twins have been investigated in relation to the occurrence of lung cancer.

LIMITATIONS OF TWIN STUDIES

There are therefore limitations in what has been, and can be, learned from twin studies. One obvious practical difficulty is the collection of large unbiased series of twins. Other factors limiting the value of twin studies include the following: (1) Differences in intra-uterine environment cannot be assessed. (2) The survival rate of both of DZ twins is higher than that of MZ. (3) There is a greater disparity between the birth-weights of MZ than of DZ pairs. Such disparity might seriously influence subsequently determined differences between the individuals of a pair. (4) Mirroring is common in, although not confined to, MZ twins and presents a complicating factor.

SUMMARY

Twin studies are informative but not necessarily conclusive. They show the remarkable degree to which the influences of heredity and environment are difficult to separate because they are interwoven. To quote Waardenberg, 'every phenotype is the reaction to peristatic and endostatic environmental stimuli'. Probably MZ twins are the most fruitful to study. They tell us the range of modificability of particular phenotypes; they may also tell us which clinical conditions can coexist and which not; they may demonstrate the relative values of different therapies in the same condition. Further, discordances in MZ twins may be of more importance than concordances, in pointing out where attention must be concentrated to gain further knowledge.

A PRACTICAL GUIDE TO THE BOTTLE FEEDING OF HEALTHY INFANTS

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THE calculation of the quantity and composition of individual bottle feeds for healthy infants is still all too often shrouded in unjustified mysticism. The procedures used vary greatly and range from mere intuition or strict adherence to instructions on the tin to methods involving calculations of not inconsiderable mathematical complexity. That such confusion should still prevail largely derives from the fact that in textbooks and other relevant publications this aspect of infant feeding is either inadequately considered or rendered unduly complicated. Yet, the practical day-to-day management of artificial feeding of healthy infants is one of considerable importance to all members of the medical and nursing professions who may be called upon for their advice.

The present account constitutes an attempt to outline a practical scheme for calculating the quantity and composition of individual bottle feeds. Although the scheme refers to babies who are entirely artificially fed it can be readily applied to complementary feeding as well. Only the feeding of healthy mature babies living in temperate climates is considered. The technique of bottle feeding is not discussed. It must be emphasized that the scheme is intended as a guide only, and should not be interpreted as providing a set of inflexible rules.

GENERAL OBSERVATIONS

The primary aim of artificial feeding must be to provide a diet adequate in both the quantity and quality of its ingredients so as to satisfy both the infant's hunger and his nutritional needs. It is essential, however, to recognize that, as with adults, these requirements vary from baby to baby. It is still not generally appreciated that of the feeding problems encountered in otherwise healthy babies, underfeeding is by far the most common single contributory factor. Although previously regarded as of common occurrence, troublesome symptoms caused by overfeeding are in fact rarely encountered. Equally exceptional in my experience are clinical disturbances due to fat, carbohydrate or protein intolerance. The practice of treating feeding problems by weakening or altering, often in minute detail, the composition of the feed is therefore, with few exceptions, therapeutically unsound.

The recognition of these facts is fundamental to the construction—and correct application—of any bottle-feeding scheme. In addition, such a

scheme should ideally fulfil the following requirements. In the first place it should be as simple as possible. Secondly, because relatively few homes are equipped with refrigerators it should provide primarily for the making up of separate and not 24-hour bulk feeds. Thirdly, to be of universal use it should embody methods of calculation applicable to available brands and varieties of milk foods suited to the feeding of healthy babies.

BASIC NUTRITIONAL NEEDS

The following are the usually recommended average daily fluid, calorie and protein requirements of infants:—

Fluid: 2½ ounces per pound (156 ml. per kg.) body weight per day.
Calories: 50 per pound (110 per kg.) body weight per day.
Protein: 1½ to 2 g. cow's milk protein per pound (3.3 to 4.4 g. per kg.) body weight per day.

Two points must be emphasized. In the first instance it must be appreciated that, whilst these average estimates serve as a useful basis for calculating artificial feeds, they should *not* be interpreted as representing accurately the needs of every individual baby. Secondly, consideration of protein needs should always be included in any such assessment. All too often, an infant's essential nutritional requirements are discussed in terms of calories and fluid only.

It is apparent that a milk feed containing 2.5 per cent. protein or more (>0.7 g./ounce) and possessing a caloric value of 20 per ounce (70 per 100 ml.) will automatically provide the requisite needs of both protein and calories, as well as fluid, when prescribed in quantities of 2½ ounces per pound (156 ml. per kg.) body weight per day. Upon this fact is based the following scheme for preparing infant feeds.

METHODS OF RECONSTITUTING MILK FEEDS

Cow's milk is available in three forms: fresh, dried and evaporated. As explained, the object of the present scheme is to reconstitute milk feeds so that the resultant mixture will provide approximately 20 calories per ounce and contain a minimum of 2.5 per cent. protein. The recommended method of reconstituting these feeds and the approximate composition of the resultant mixture are summarized in table I.

No special form of sugar is needed. The ordinary household granulated form of cane sugar is perfectly suitable.

FRESH COW'S MILK

An average sample of undiluted cow's milk contains about 3.5 per cent. protein, 3.5 per cent. fat and 4.5 per cent. carbohydrate, and so has a caloric value of 18 per ounce. The caloric value may be increased to 20 per ounce by adding sugar in the proportion of one level teaspoon to 8 ounces (227 ml.) milk. The carbohydrate content of the milk will thus be raised by slightly

less than 2 per cent. and the calories by about 2 per ounce (1 level teaspoon of sugar = 15 cals.).

If a diluted milk feed is required the following is recommended:—

Three parts of cow's milk to 1 part of water, 1 teaspoon of sugar to every 2½ ounces (71 ml.) of the milk mixture. Without the addition of sugar the diluted milk would have the following composition: protein 2.6 per cent., fat 2.6 per cent., carbohydrate 3.4 per cent. and calories 13.5 per ounce. By adding sugar in the proportion suggested the carbohydrate content will be raised by 5 per cent. to 8.4 per cent. and the caloric value by 6 per ounce to 19.5 per ounce.

More dilute mixtures have the great disadvantage of a low protein content. Such feeds, moreover, require the addition of large quantities of sugar to correct the caloric deficiency created by dilution.

DRIED MILK FEEDS

(a) *Full-cream.*—(Available preparations: Cow and Gate Full Cream, Trufood Spray-dried Full Cream, Dorsella, Ostermilk No. 2, Cockade Full Cream Spray-Dried, Nespray Spray-Dried Full Cream, National Dried

Food*	Dilution factor (milk food:water)	Addition of sugar (level teaspoons sugar: ounces milk mixture)	Approximate composition of reconstituted feed†			
			Protein (%)	Fat (%)	Carbohydrate (%)	Calories per ounce
Fresh cow's milk						
Undiluted	—	1:8	3.5	3.5	6.5	20
Diluted	3 ounces: 1 ounce	1:2½	2.5	2.5	8.5	20
Dried milks						
Full-cream (i)	1 measure: 1 ounce	1:8	3.5	3.5	6.5	20
(ii)	¾ measure: 1 ounce	1:2½	2.5	2.5	8.5	20
Half-cream (i)	1 measure: 1 ounce	1-4	4.0	2.0	8.5	20
(ii)	1¼ measure: 1 ounce	—	3.0	2.5	8.5	20
Evaporated full-cream unsweetened	1 ounce: 2 ounce	1:4	3.0	3.0	7.0	20

*For proprietary foods corresponding with each type of milk food see text.
†Approximate figures only have been quoted intentionally. In view of differences in quality of fresh cow's milk samples, minor differences in composition between proprietary brands of the same type of milk food and inaccuracies resulting from the use of relatively crude domestic measures, it would be unrealistic to attempt a more exact analysis.

TABLE I.—Reconstitution of milk feeds.

Milk Full Cream.) All these milks, irrespective of the proprietary brand, when reconstituted by mixing one level measure (scoop) of powder with 1 ounce of water yield a milk mixture with about the same quantitative composition as fresh cow's milk: i.e. protein 3.5 per cent., fat 3.5 per cent., carbohydrate 4.5 per cent. and calories 18 per ounce. The caloric value of the feed is raised to 20 per ounce by adding one level teaspoon of sugar to

every 8 ounces of milk mixture. (Note: Measures (scoops) for measuring out dried milk powder are not interchangeable.) As with fresh cow's milk a similar low-fat mixture can be prepared. This is done by adding ¾-measure of milk powder to each ounce of water and adding one level teaspoon of sugar for every 2½ ounces of milk mixture (table I—Full Cream Dried Milk (ii)).

(b) *Half-cream.*—Two distinct types of half-cream dried milks have to be considered.

Type i (*unsweetened*).—Two foods only are included in this group. They are National Dried Milk Half Cream and Cow and Gate Special Half Cream. When reconstituted by mixing 1 level measure with 1 ounce of water the resultant mixture has the following approximate composition: protein 4 per cent., fat 2 per cent., carbohydrate 5.5 per cent. and calories 16 per ounce (56 per 100 ml.). Additional calories are provided by adding sugar, 1 teaspoon to every 4 ounces of milk mixture. This has the effect of raising the carbohydrate content of the feed to about 8.5 per cent. and the calories to 20 per ounce (70 per 100 ml.).

Type ii (*sweetened*).—Included in this group are Ostermilk No. 1, Cow and Gate Half Cream, Trufood Half Cream. On mixing 1 level measure of these feeds with 1 ounce of water the resultant mixture has the following approximate composition: protein 2.4 per cent., fat 2 per cent., carbohydrate 7 per cent. and calories 16 to the ounce. Made up in this manner these feeds are clearly deficient in calories and borderline in protein. The addition of sugar is not recommended. In the first place, this would leave the protein content unaltered. Secondly, the amount of sugar needed to raise the caloric value to 20 per ounce (70 per 100 ml.) would mean increasing the carbohydrate content to 11 per cent.

In order to provide a feed adequate in both protein and calories, these feeds should be reconstituted by mixing 1¼ level measures to each ounce of water. The approximate composition of such a mixture is as follows: protein 3 per cent., fat 2.5 per cent., carbohydrate 8.5 per cent. and calories 20 per ounce.

EVAPORATED MILK FEEDS

Only unsweetened forms are suitable for feeding healthy babies, e.g. Carnation Milk, Libby's Evaporated Milk, Nestle's Ideal Full Cream Evaporated and Regal Evaporated Milk. These feeds should be made up by mixing 1 ounce of milk with 2 ounces of water and adding a level teaspoon of sugar to every 4 ounces of mixture. The final composition of the feed approximates to protein 3 per cent., fat 3 per cent., carbohydrate 7 per cent. and calories 20 per ounce.

CHOICE OF FOOD

The choice of food is largely a matter for maternal or individual medical preference. Babies will progress perfectly satisfactorily irrespective of the

proprietary brand or type of milk food used (i.e. fresh, evaporated or dried), provided the selected food is given in adequate quantity and correctly reconstituted. In practice the ultimate choice is probably more commonly determined by such factors as availability, familiarity, prevailing local customs and policy or convenience, rather than by any special nutritional advantage of the food itself.

During the first few weeks of life the absorption of cow's milk fat may be impaired. This rarely causes any troublesome digestive upset. More important is the loss to the infant of calories. Almost 50 per cent. of the calories provided by a reconstituted full-cream milk are supplied by fat. Thus, an infant fed on a full-strength full-cream feed will be deprived of many essential calories should a large proportion of the fat not be absorbed. For this reason I prefer, as a routine, to feed babies during the early weeks on half-cream milk mixtures.

There is a prevalent, though misguided, view that to designate a feed as half-cream is synonymous with saying that it is of weaker composition than a full-cream feed. Reference to table I shows that, in fact, if correctly reconstituted both types of half-cream dried milk are of comparable food value to full-cream feeds, the essential difference being that relatively more calories are supplied by fat in full-cream (45 per cent.) than in half-cream milk mixtures (25 to 30 per cent.).

QUANTITY OF FEED

The daily quantity of food to be offered should be calculated on the basis of weight and should not be determined by age. As already stated, 2½ ounces per pound (160 ml. per kg.) body weight in twenty-four hours serves as a useful guide to fluid requirements. Although it is commonly recommended that calculations should be based on the infant's expected weight, it is better to confine this policy to infants who are underweight. In other instances the actual weight affords a better guide. In other words, an infant should be fed for whichever is the greater of the two weights, actual or expected. In the case of infants who are considerably underweight it is as well to compromise initially and feed for a weight intermediate between the two.

To avoid unnecessarily complicated fractions the nearest whole pound above the greater of the two weights, actual and expected, should be used for calculating the quantity of feed. For example, an infant weighing 7 pounds 10 ounces, whose expected weight was 7 pounds 2 ounces, would in practice be fed for 8 pounds.

CALCULATIONS OF EXPECTED WEIGHT

Most babies lose weight during the first few days following birth. With few exceptions, this drop in weight has been regained by the tenth day. Thereafter, an infant can be expected to gain at least 1 ounce (28 g.) a day up to 3 months of age (90 days). An increase in weight of 1 pound (450 g.)

a month affords a useful guide to progress between 3 and 12 months. Whilst these figures are helpful in assessing progress they should not be interpreted as indicating the optimum rate of growth during infancy. In fact, provided they are adequately fed most infants will gain weight more rapidly than this.

Using these average figures, the expected weight of a baby is determined as follows:—

(i) *If under 3 months.*—Expected weight = birth weight + (age in days—10) ounces.

Example.—A 2-month (60 days)-old infant whose birth weight was 7 pounds 6 ounces would be expected to weigh 7 pounds 6 ounces + (60—10) ounces = 10 pounds 8 ounces.

At 3 months (90 days) this same baby's expected weight would be 7 pounds 6 ounces + (90—10) ounces = 7 pounds 6 ounces + 5 pounds = 12 pounds 6 ounces.

(ii) *If aged between 3 and 12 months.*—Expected weight = birth weight + 5 (expected weight gain by 3 months. See previous example) + (age in months—3) pounds.

Example.—The expected weight of an infant aged 9 months and who weighed 6 pounds 10 ounces at birth would thus be 6 pounds 10 ounces + 5 + 6 = 17 pounds 10 ounces.

ARTIFICIAL FEEDING DURING THE FIRST WEEK

A rough guide to the feeding requirements during the first week of life may be summarized as follows:—

Age (days)	Feed	
1	Sterile water	
2, 3	¼ strength	of
4, 5	½ strength	chosen
6, 7	¾ strength	milk
>7	Full strength	food

Total daily quantity of feed = $2\frac{1}{2}$ ounces x weight in pounds x $\frac{\text{age in days.}}{.7}$

SPACING AND VOLUME OF INDIVIDUAL FEEDS

So as to enable a mother to plan her days' activities to the best advantage it is desirable to effect a regular, though flexible, feeding routine. In practice most healthy babies can be fed to an *approximate* four-hourly feeding schedule. This implies giving five feeds in the day. In some instances, during the first weeks and with small infants (less than 6 pounds [2.7 kg.]) a three-hourly schedule may be preferred. In such cases, six feeds are offered in the twenty-four hours.

The volume of each individual feed is determined by dividing the twenty-four-hour requirements by either 5 or 6, depending upon the schedule used. If the baby is being fed four-hourly the volume of each feed can be rapidly determined by the simple expedient of halving the weight (in pounds). This gives the volume of each feed in ounces, e.g.:—

For a baby being fed for 10 pounds weight, the volume of each feed on a four-hourly × 5 schedule = $\frac{10}{2}$ = 5 ounces.

This feeding schedule takes no account of night feeds. If needed, an addi-

tional identical feed to that given during the day can be offered. Extra night feeds are seldom necessary, however, after the first week or so provided the baby is being adequately fed and the last feed of the day is given as late as possible: i.e. shortly before mother retires to bed.

Whilst these instructions afford a satisfactory guide to the infant's requirements they are not meant to be rigidly adhered to. Whenever an infant appears unsatisfied it is a good policy to offer more. Conversely, babies should not be forced, against their will and better judgment, to take all of any single feed offered. Mothers should be warned that amounts taken at each feed may vary.

MAKING UP INDIVIDUAL FEEDS

Having first determined the volume of each feed these are then made up as required according to the recommended scheme summarized in table I. This can best be illustrated by reference to an example.

A baby who is being fed four-hourly for 8 pounds (3.5 kg.) would be offered 4-ounce (115 ml.) feeds. If undiluted fresh cow's milk is to be used each feed would consist of 4 ounces (115 ml.) of milk to which had been added ½-teaspoon of sugar. If it is decided to use a full-cream dried milk (e.g. Cow and Gate Full Cream) each individual feed would be made up by mixing 4 level scoops of powder in 4 ounces (115 ml.) of water and adding ½-teaspoon of sugar. Assuming the baby is to be fed on a half-cream dried milk corresponding with type (i) (e.g. National Dried Milk Half Cream), each feed would be made up by mixing 4 scoops of powder in 4 ounces (115 ml.) of water and adding 1 teaspoon of sugar. If a type (ii) half-cream dried milk was being used (e.g. Ostermilk No. 1), 5 level scoops of powder would need to be added to 4 ounces (115 ml.) of water; no sugar would be required.

Inevitably there will be occasions when small fractions of an ounce are involved.

For example, a 5½-ounce feed given in the form of a diluted fresh cow's milk mixture would involve mixing 4⅛ ounces cow's milk with 1⅜ ounces water. Similarly, if the infant was being fed on an unsweetened evaporated milk mixture the quantities of evaporated milk and water needed to make up a 5½-ounce feed of the correct composition would be 1⅛ ounces and 3⅜ ounces. This is obviously impractical.

To avoid using such small fractions, feeds should be calculated for the nearest convenient volume *above* that theoretically required. In each of the two examples cited, 6-ounce feeds should be offered in place of the estimated 5½ ounces. The correct dilution of cow's milk would then be obtained by adding 4½ ounces of milk to 1½ ounces of water and the evaporated milk feed would be made up by mixing 2 ounces of evaporated milk with 4 ounces of water.

The final step in the reconstitution of each feed is the addition of sugar. The domestic method of measuring with a teaspoon renders absolute accuracy impossible. This is of little consequence as strict accuracy is not important. Quantities should be quoted to the nearest quarter.

APPLICATION OF SCHEME

Four steps are involved in working out the quantity and composition of each bottle feed:—

(1) Calculation of the expected weight and comparison with the infant's actual weight.

(2) Estimation of the total fluid intake per twenty-four hours.

(3) Calculation of the volume of each feed. If the baby is fed four-hourly, step 2 can be omitted as each feed in ounces will equal half the weight recorded in pounds.

(4) Reconstitution of feeds as set out in table I.

Example.—A 6-week-old infant (birth weight 6 pounds 7 ounces [2.9 kg.]) weighs 8 pounds 10 ounces (3.9 kg.) and is being fed four-hourly. The baby's expected weight is therefore 8 pounds 7 ounces (3.8 kg.). To avoid small fractions, the baby will be fed for 9 pounds (4 kg.) and each feed offered will be of $4\frac{1}{2}$ ounces (128 ml.) or more.

Depending upon the choice of food each feed will be made up as follows:

Food	Measures (or ounces) of milk food	Water (ounces)	Sugar (tea-spoons)	Volume of feed (ounces)
Fresh cow's milk	$4\frac{1}{2}$	—	$\frac{1}{2}$	$4\frac{1}{2}$
Diluted fresh cow's milk	$3\frac{3}{4}$	$1\frac{1}{4}$	2	5
Full-cream dried milk	$4\frac{1}{2}$	$4\frac{1}{2}$	$\frac{1}{2}$	$4\frac{1}{2}$
Diluted full-cream dried milk	$3\frac{3}{4}$	5	2	5
Half-cream dried milk, type (i)	$4\frac{1}{2}$	$4\frac{1}{2}$	$1\frac{1}{4}$	$4\frac{1}{2}$
Half-cream dried milk, type (ii)	$6\frac{1}{4}$	5	—	5
Evaporated unsweetened milk	$1\frac{1}{2}$	3	$1\frac{1}{4}$	$4\frac{1}{2}$

The scheme can be applied equally well to the preparation of twenty-four-hour bulk feeds should suitable facilities exist.

SUMMARY

A scheme is outlined for calculating the quantity and composition of individual bottle feeds irrespective of the type of milk food used.

The particular merits of different milk preparations are not discussed.

The object of the scheme is to ensure that whatever food is chosen it shall be suitably reconstituted and provided in adequate quantity.

DEQUALINIUM IN THE TREATMENT OF TRICHOMONIASIS IN WOMEN

By D. R. LEVINSON, M.B., B.S.

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THE high antimicrobial activity present in polymethylene-bis-*iso*-quinolinium salts led Babbs *et al.* (1956) to investigate a large number of related compounds for their antimicrobial activity. The compound, decamethylene-bis-(4-aminoquinaldinium), was found to have wide antimicrobial activity *in vitro;* it inhibited the growth of all the species of pathogenic bacteria that were tested including gram-positive, gram-negative, penicillin-resistant and acid-fast bacteria. Furthermore, similar activity was shown against certain yeasts and fungi, notably, *Candida albicans*, *Microsporum canis*, *Trichophyton mentagrophytes*, *Trichophyton rubrum* and *Trichophyton verrucosum*. This new synthetic antimicrobial compound has been given the Approved Name of dequalinium, and is also available as 'dequadin'. Its extremely low toxicity and the absence of local irritation on mucous membrane and skin was shown by laboratory experiments on mice and rabbits. Solutions containing 2 mg. of dequalinium per ml. of saline appeared to be without effect on the eyes of rabbits when instilled daily for two weeks. Creams containing 0.4 per cent. were applied daily for four weeks to the shaved skin of rabbits and to hairless mice without any reaction. Administered orally in 5 per cent. suspension in water, 2 grammes per kilogram, dequalinium failed to kill any mice in the series of 20 tested. Rats receiving 0.05 per cent. in their drinking water for twenty-six weeks survived and showed no depression of growth compared with controls. That the therapeutic activity of dequalinium is essentially local was pointed out by Babbs *et al.*, who showed that in mice infected intraperitoneally with virulent cocci, it was effective when given intraperitoneally but not when given subcutaneously. Clinical reports on the local application of dequalinium have borne out the laboratory findings (Wilkinson, 1959).

This compound evoked my interest in the treatment of trichomoniasis in the female, as it appeared to be the first non-antibiotic substance which is claimed to inhibit the growth of nearly all common pathogenic bacteria found in the vagina, as well as yeasts and, at the same time, to be non-toxic to human tissue. Whilst it is admitted that the treatment of trichomonal infections by local application has proved unsatisfactory in the past, it is submitted that the eradication of *Trichomonas vaginalis* rests more with the restoration of the normal bacterial flora and consequent production of an

acid pH than perhaps with the actual extermination of the trichomonads. It was with this end in view that dequalinium was selected for clinical evaluation.

SCOPE OF INVESTIGATION

The effect of dequalinium was investigated in 43 women between the ages of 14½ and 55 years who had previously failed to respond in any satisfactory degree to any other forms of orthodox treatment including the use of pessaries containing oxytetracycline.

The symptoms most commonly complained of were those of vaginal discharge and irritation; only a few complained that the discharge was offensive. Others presented with intolerable irritation of the vulva, but very little vaginal discharge. No cases of bartholinitis were seen although several had infection of the para-urethral ducts. One case on examination revealed a cervical polyp and in another, carcinoma of the vaginal wall. Two married women complained of the onset of dyspareunia, and in three cases the male consort presented with a purulent urethritis in which *Trichomonas vaginalis* was present in large numbers. All cases in this series were of marked chronicity. Both married and unmarried women were implicated. Two patients had venereal infection; one was infected in the urethra only with *Trichomonas vaginalis* as evidenced by the wet-slide method.

Method of diagnosis.—This was made in the clinic and at the time of examination by the wet-slide method using dark ground illumination. Specimens were taken from the posterior fornix and from the urethra by means of a loop. Whenever the patient had actual symptoms it was found that in the majority of cases there was a large number of pus cells present and lesser numbers of *E. coli* and usually a marked absence of Döderlein's bacilli. About 40 per cent. of patients had a measure of 'mixed' organisms present.

Progress was judged by diminution in the symptoms and improvement in the pus:squame ratio. It often took many weeks for the normal bacterial flora to become re-established and in chronic cases this failed to occur even after months of continuous treatment in the older women.

METHOD OF TREATMENT

Douching was forbidden at any time since, in my opinion, the introduction of so-called antiseptics into the vagina destroys or upsets the normal bacterial flora, which is conducive to *Trichomonas vaginalis* infestation, apart from the risk of reinfection from the douche nozzle.

The patient was instructed to insert a 'dequadin' pessary each night and morning, when in the approved position: i.e. supine with knees drawn up. Treatment was continued for a period of one month, care being taken to ensure that it was continued throughout the menstrual period. At the end of the first ten days the patient was re-examined and the number of *Tri-*

chomonas vaginalis per field was noted, together with any change in the cytology and bacteriology. The course was continued, however, even if *Trichomonas vaginalis* was not demonstrated in the specimens.

RESULTS

All but one patient obtained marked and rapid relief from symptoms within twenty-four to seventy-two hours of starting treatment. In only approximately 40 per cent. of cases, however, was there complete clearance of symptoms, with disappearance of *Trichomonas vaginalis*, and some return of Döderlein's bacillus was seen. If left without further treatment some of these cases relapsed after varying periods of from two to sixteen weeks but all except one were brought under control rapidly by reinstitution of treatment. All except one reported that this was the first time that they had any measure of comfort and in the one case in which exacerbation of symptoms had occurred, the microscopical findings in no way suggested that any deterioration in the cytology of the vagina had occurred and the number of *Trichomonas vaginalis* present was greatly diminished. Only one patient complained of the pessary substance running out on rising, and four cases of non-specific vaginitis, all showing alpha-hæmolytic streptococci, cleared rapidly when 'dequadin' pessaries were used. Two cases of severe moniliasis following oral antibiotic therapy were also rapidly cleared.

This clinical trial is still proceeding, and since this report was written 21 further patients have been treated, including two with monilia infection, with comparable results.

SUMMARY

The effect of dequalinium, in the form of 'dequadin' pessaries, has been studied in 43 women, aged 14½ to 55 years, with *Trichomonas vaginalis* infestation.

Complete eradication of *Trichomonas vaginalis* occurred in only 40 per cent. of cases of marked chronicity. In the remaining cases all the clinical symptoms were greatly diminished.

All but one patient obtained marked and rapid relief from symptoms within twenty-four to seventy-two hours of inserting the pessary and in those cases in which *Trichomonas vaginalis* was still present the pus:squame ratio had improved and some return of Döderlein's bacilli was seen.

A number of cases relapsed after varying periods of from two to sixteen weeks but all except one were brought under control rapidly by reinstitution of treatment with dequalinium.

I am indebted to Allen & Hanburys Ltd. for the supply of 'dequadin' pessaries used in this trial.

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BERRIES—POISONOUS AND EDIBLE

By DOUGLAS HENDERSON, B.Sc.
Royal Botanic Garden, Edinburgh

'The commonest symptom of yew poisoning is sudden death'—so writes an authority on poisonous plants, adding emphasis, if any is required, to the need for speedy and accurate identification of plants involved in cases of suspected poisoning. Berries, frequently brilliantly coloured and highly attractive, especially to children, are most commonly implicated.

IDENTIFICATION

If a complete plant is available recourse may be made to a standard flora, e.g. 'Flora of the British Isles' (Clapham, Tutin and Warburg, 1952), used in conjunction with 'Illustrations of the British Flora' by Fitch and Smith (1939). Often, however, only the berries or portions of them in stomach contents may be available but even they may be identified within certain limits, especially if the patient can give some details of the plant from which the berries came: where it grew, in hedgerow or moorland, or whether it was a low herb or tall shrub. It may often be a matter of considerable detective work to discover the plant involved and on-the-spot investigation may more quickly give the answer. Fears of poisoning are dispelled if the berries prove to be harmless, whilst the most appropriate remedies may be applied immediately if the plant proves dangerous. The other approach to treatment in cases of plant poisoning, that via diagnosis from patient symptoms, and the particular course of treatment must be left outside a botanist's sphere. Laying aside therefore the question of symptoms of specific poisons, what are the commonly occurring berried fruits of Britain and how may the identity of berries be determined from purely botanical characters? It should be noted at the outset that the term 'berry' must be used in the very widest sense to include any fleshy fruit and not merely the restricted connotation given to it by botanists. With a few exceptions the berries commonly occurring in Britain are either red or blackish when ripe; but of course all are greenish when young and in this state even the most edible can cause illness when eaten. Indeed, berry colour is certainly the most convenient primary division of berries for their recognition.

BLACK POISONOUS BERRIES

Among the black-coloured berries the most feared—and justifiably so—are those of the *deadly nightshade* (*Atropa belladonna*) (fig. 1). Three berries are quite sufficient to kill a child. The plant usually grows in semi-shaded sites with annual, branching stems up to three feet high. The ovate leaves occur in pairs on one side of the stem; one of the pair usually conspicuously larger than the other. The dingy purple, drooping, bell-shaped flowers with

triangular green calyx lobes occur from June onwards. The berries, ripe from July, are dull black, almost spherical, often as large as a small marble, and are surrounded by the persistent withered calyx. Within the rather dry fruit is a number of seeds. The fruits of the potato are very similar in shape

FIG. 1.—Atropa belladonna.

FIG. 2.—Rhamnus frangula.

and structure but lack the conspicuous calyx lobes. They are equally poisonous, containing the same principle—solanine.

A less common but extremely poisonous plant the *baneberry* (*Actæa spicata*) grows in woods on limestone in Yorkshire, Lancashire and Westmorland. The green, then black, shining, juicy fruits, nearly a quarter of an inch in diameter, are borne on stems one to two feet long with the remains of the divided leaves at the base. The berries cause severe gastro-enteritis if eaten, but the comparative rarity of the plant renders it of minor importance. Somewhat more common is *Herb Paris* (*Paris quadrifolia*) growing usually in semi-shade. The stems up to two feet high bear single whorls of leaves at the apex surrounding inconspicuous yellow-green flowers which later yield single, slightly lobed, purplish-black, juicy fruits up to a quarter of an inch in diameter which contain sixteen to twenty dark-coloured seeds.

In woody thickets, usually on peaty soil, grow the *buckthorn* (*Rhamnus cathartica*) and the *alder buckthorn* (*Frangula alnus* or *Rhamnus frangula*) (fig. 2), shrubs up to twenty feet high. The leaves have characteristically curved, sub-parallel veins and both species have clusters of inconspicuous flowers and globose black berries about the size of blackcurrants which are reminiscent of those of the birdcherry or the cherry laurel. But whereas the cherry type has only one seed, both buckthorns have four per fruit. Both buckthorns act as violent purgatives and are especially dangerous for children. Cascara sagrada is prepared from the bark of another member of the genus, *Rhamnus purshiana*.

Common throughout the country, but less commonly seen in flower and fruit owing to their use in hedges, are the *privets* (*Ligustrum vulgare* [fig. 3] and *Ligustrum ovalifolium*). Only on unpruned plants do the masses of white flowers and small black globular berries form in quantity. Each berry

FIG. 3.—Ligustrum vulgare.

FIG. 4.—Hedera helix.

is about the size of a pea with two chambers inside, usually with one or two seeds in each. These berries, so easily accessible to children, have caused fatal poisoning.

The kernels of many of our most attractive fruits, including cherry, plum, almond and apricot, contain a certain proportion of amygdalin, a cyanogenic glycoside which yields hydrocyanic acid on enzymatic breakdown; but, of course, unless the contents of the kernel are chewed they are not a cause of trouble. In the *cherry laurel* (*Prunus laurocerasus*), however, this substance is present in the leaves and flesh of the fruit and presents a more likely source of poisoning. Cherry laurel is commonly grown in gardens and parks where it develops as a rather coarse shrub with thick, leathery, evergreen leaves. It bears tassels of white, scented flowers and in late Summer small, black, spherical berries very like small, black cherries except that the fruit stalk is short and rigid and the fruits, up to about twelve in number, are borne along a common inflorescence stalk four inches long. Within the fruit is a single 'stone' just as in the related cherry and plum. In woodlands in England the *spurge laurel* (*Daphne laureola*) occurs sparingly. The inconspicuous greenish flowers are borne below clusters of shining evergreen leaves on sparingly branched stems up to four feet high. The blue-black berries are egg-shaped and very poisonous.

The *ivy* (*Hedera helix*) (fig. 4) is curious in that its dingy greenish-white flowers appear in early Winter from October to December and the blackish berries, globular and about the size of a pea, are ripe in early Spring.

Adults are not liable to confuse them with any edible fruit at this season but their potential danger to children remains, and although the fruits are not extremely poisonous they act as violent purgatives. Among black-berried fruits, the *elder* (*Sambucus nigra*) holds an intermediate position. It is

FIG. 5.—Solanum dulcamara.

FIG. 6.—Tamus communis.

commonly used in making preserves and wine but there is some evidence that eaten raw it can act as a rather violent purgative, although cases of more serious poisoning are not forthcoming.

RED POISONOUS BERRIES

Whilst black-coloured berries may lead to confusion and poisoning, the chance is even greater with red-berried plants as their number is greater and, of course, the colour tends to attract children more readily. Particularly along hedgerows and on waste ground is there a number of poisonous, red-berried plants. Several are weak, straggling, plants such as the *woody nightshade* or *bittersweet* (*Solanum dulcamara*) (fig. 5). With attractive purplish flowers reminiscent in form of those of a potato or tomato, its weak stems scramble over other plants and die down each Winter. The lower leaves are dark, glossy green, three-lobed with the centre lobe the largest; the upper leaves are heart-shaped and entire. The berries, borne in clusters six to eight together, are bright-red, translucent—very like red-currants except that there is no tuft of old flower parts at the upper end of the fruit—and there are numerous seeds within, compared to the six or eight in the redcurrant. The woody nightshade is common in South and Central England becoming more scarce farther North. The berries and all parts of the plant contain the same poison, solanine, as the deadly nightshade.

Two other poisonous scrambling plants of wayside and wasteland deserve mention; both are most frequent in Southern England and almost entirely absent in the North. The *white bryony* (*Bryonia dioica*) is a vigorous, hairy

plant with twining tendrils and leaves deeply divided into five to seven segments. The flowers are yellowish-green, rather inconspicuous and the fruits dull scarlet, globular, berries about one centimetre in diameter with three to six large, flat, yellow-and-black mottled seeds within. The *black*

FIG. 7.—Arum maculatum.

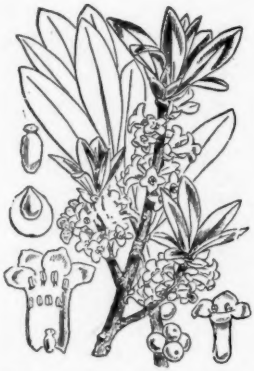

FIG. 8.—Daphne mezereum.

bryony (*Tamus communis*) (fig. 6), although similar in name, habit and poisonous properties, is not closely related to the white. Its long straggling stems are quite smooth, the leaves simple and undivided, and the unisexual flowers greenish and inconspicuous. The bright crimson, translucent berries borne in small bunches are superficially like redcurrants. It could most easily be mistaken for the woody nightshade but can be distinguished by the simple leaves on the lower part of the stem.

In thicket, scrub and woodland grows another group of red-berried poisonous fruits. Most conspicuous perhaps is the *cuckoo-pint* or *lords and ladies* (*Arum maculatum*) (fig. 7). It occurs abundantly in damp woodlands, sometimes in hedgerows, especially on basic soils. In Spring and early Summer the curious, sheathed flower clusters and the arrowhead-like leaves on long stalks are quite characteristic. The bright-red berries—reminiscent of those of the mountain ash—ripe from August onwards—cluster eight to twenty together at the upper end of a sturdy, naked, green stem about six to nine inches long. By the time the berries are ripe the leaves have withered completely, although a few remains may aid identification. The berries themselves, about the size of a pea, bear three small marks at their apex and usually contain three brownish, rough-coated seeds.

One plant in the wild state uncommon in Southern English woodlands and absent farther north but commonly cultivated in gardens is the *mezereon* or *dwarf bay tree* (*Daphne mezereum*) (fig. 8). The whole plant, including its red berries, is intensely poisonous as is its near relative the black-berried spurge laurel. Mezereon is prized in gardens for the early appearance of its

heavily scented, pink or purplish flowers from January onwards. The flowers are borne in small clusters on the bare branches. The simple spatulate leaves appear in tufts at the ends of the branches; beneath them the red berries are grouped in small clusters and are ripe from August onwards.

FIG. 9.—Taxus baccata.

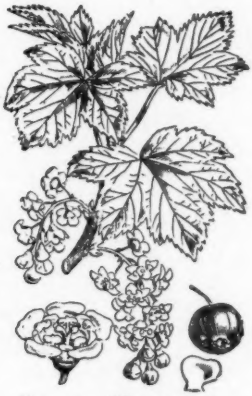

FIG. 10.—Ribes rubrum.

When they have been responsible for poisoning they have usually been mistaken for redcurrants but can be distinguished by the lack of a tuft of withered flower parts at the upper end of the fruit—so characteristic of all the currants.

Finally among the poisonous red berries, is the *yew* (*Taxus baccata*) (fig. 9) of whose poisonous properties there is probably more general awareness than of any other, but whose temptation to children is great. It is widespread naturally in Southern Britain but is planted widely elsewhere for ornament, particularly as hedges or in churchyards. Indeed it is held that yews commonly occur in churchyards due to the early need to grow them for bow wood and at the same time keep them away from cattle and children—the foliage is also intensely poisonous. On the dark, evergreen branchlets the fruit is ripe from August onwards. The pale, half-inch-long seed is half submerged in a soft, red, juicy cup. This fleshy cup is rather sickly sweet and not itself particularly poisonous but the seed is highly toxic due to its content of the alkaloid complex, taxine.

EDIBLE BERRIES

If commonly grown garden plants are included, the number of berried fruits in Britain is very high and by far the great majority are harmless—at least if eaten in reasonable quantities. It is superfluous to mention the commonly cultivated berried fruits—the currants—except to add a reminder that both *redcurrants* (fig. 10) and *blackcurrants*, especially the former, and the *gooseberry* do grow wild in Britain and are also often semi-wild as escapes from cultivation, and may be confused with the poisonous bryonies,

woody nightshade and mezereon. The *wild blackberries* and *raspberries*, also, with their cultivated relatives are, of course, quite harmless.

It is convenient to note that none of the berried fruits of heathlands and mountains is poisonous. This group includes the purplish *whortleberry* or

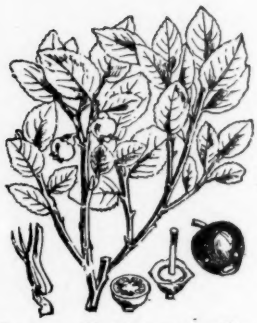

FIG. 11.—Vaccinium myrtillus.

FIG. 12.—Rosa canina.

bilberry (*Vaccinium myrtillus*) (fig. 11), the bright-red *cowberry* or *red whortleberry* (*Vaccinium vitis-idaea*), the black *crowberry* (*Empetrum nigrum*), the large, purplish-black *bearberry* (*Arctostaphylos uva-ursi*), the bog-dwelling *cranberry* (*Oxycoccus palustris*) with brownish mottled fruits, as well as the rarer *cloudberry* (*Rubus chamaemorus*) and *alpine bearberry* of the North-West Highlands (*Arctous alpinus*). With this group belongs also the *juniper* (*Juniperus communis*) with pale bluish-black fruits—an inhabitant of similar habitats to those mentioned above but also occurring on chalk and limestone grasslands.

In hedgerows the *barberry* (*Berberis vulgaris*), with its very spiny stems, simple obovate leaves and tassels of yellow flowers, bears in Autumn, elliptical, waxy, berries, each with a single seed—the whole quite harmless. Indeed, the spread of the plant is probably due to its former more widespread use in making preserves. The straggling, twining stems of *honeysuckle* (*Lonicera periclymenum*) with clusters of shining, red berries might be confused with those of the black or white bryony or the woody nightshade. However, the oppositely arranged leaves of the honeysuckle, its woody stems and dense clusters of stalkless berries should suffice to distinguish it. The fruits are not poisonous and the similar fruits of the many cultivated honeysuckles are apparently equally innocuous.

The harmless fruits of the *lily of the valley* (*Convallaria majalis*) are small, round, red, berries on short, nodding stalks on a short, delicate stem. They occur in similar situations to the poisonous cuckoo-pint and the two might be confused but the lily of the valley is much more delicate and graceful

in its fruiting stage. The *wayfaring tree* (*Viburnum lantana*) with softly hairy leaves, oppositely arranged on the branches, has panicles of laterally compressed berries, red at first, then turning rapidly black, just on reaching maturity. The related *guelder rose* (*Viburnum ebulus*) which, unlike its near relative, occurs throughout Britain and is not restricted to the South of England, has much smoother, thinner leaves and the berries remain red at maturity. Both species are innocuous. So too, are the wine-red to blackish fruits of the *hawthorns* (*Cratægus* spp.) each with a single stone. The orange-red fruits of the *wild roses*, including the *dog rose* (*Rosa canina*) (fig. 12), are, of course, edible but the chaffy appendages of the seeds inside may cause irritation and inflammation of the throat.

Other orange-red or scarlet fruits which are harmless are those of the *mountain ash* or *rowan* (*Sorbus aucuparia*), the *whitebeam* (*Sorbus aria*), the commonly planted *Sorbus intermedia* and the *sea buckthorn* (*Hippophæ rhamnoides*). The mountain ash, whose berries yield a rather tart jelly, is of widespread occurrence; the other *Sorbus* species are less common whilst the sea buckthorn is more or less restricted to coastal districts. One would expect the fruits of the *blackthorn* or *sloe* (*Prunus spinosa*), the *wild plum* (*Prunus domestica*) in its various forms, and the *wild cherry* (*Prunus avium*) to be edible, but the black fruits, especially of the former, could be confused with those of the deadly nightshade until attention is paid to the single stone of the *Prunus* as opposed to numerous minute seeds of the *Atropa*. The blackish-purple, very astringent, fruits of the *birdcherry* (*Prunus padus*), about a dozen on a common fruit stalk, might well be mistaken for those of the very poisonous cherry laurel. The birdcherry, however, is deciduous whilst the cherry laurel is evergreen; also the birdcherry is relatively uncommon except in the Scottish Highlands.

The white fruits of the *snowberry* (*Symphoricarpus racemosus*) are often the cause of alarm but are quite harmless. The plant occurs either in cultivation or naturalized in hedges, thickets and waste places where it bears its white pulpy berries, about the size of a marble, on slender branches in late Autumn.

CONCLUSION

Whilst the number of berried fruits in Britain is high enough to make recognition quite difficult, the inclusion of garden 'berries' makes reference to an expert imperative, although it is worth noting that many cultivated plants are harmless including the commonly encountered *Cotoneaster*, *Escallonia*, *Amelanchier* and *Pyracantha*. Some reference to them is made in 'British Poisonous Plants', Bulletin No. 161 of the Ministry of Agriculture and Fisheries, where good accounts of all poisonous plants in Britain, with special reference to livestock, are given. A further aid to identification, Sowerby's 'English Botany', in twelve volumes with coloured plates, includes descriptions of all the plants and notes on their poisonous properties.

The illustrations are reproduced by courtesy of L. Reeve & Co. Ltd., from 'Illustrations of the British Flora', fifth edition, by W. H. Fitch and W. G. Smith.

GENERAL PRACTITIONERS' FORUM

CHLOROFORM ANÆSTHESIA IN DOMICILIARY MIDWIFERY

By JOHN McCARTNEY, L.R.C.P., L.R.C.S.Ed., L.R.F.P.S.

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CHLOROFORM is said to be a very dangerous anæsthetic:—

(1) 'Chloroform is more potent than ether as a general anæsthetic. While it has the advantages over ether of more rapid induction of anæsthesia, less excitement and pulmonary irritation, less postoperative nausea and vomiting, better muscle relaxation and non-inflammability, it has the disadvantages of greater cardiac, renal and hepatic hazards' ('The Extra Pharmacopœia', 1958).

(2) Chloroform 'is a particularly dangerous anæsthetic . . . . Sometimes it kills rapidly and suddenly by stopping the heart when only a small dose has been given, and sometimes it damages the liver, heart and kidneys so that death occurs a few days later. It is still used because it is easy to administer, rapid in action and not inflammable' (Gaddum, 1953).

EXPERIENCE

For many years I have been doing maternity work in general practice, and to date the number of instrumental deliveries under general anæsthesia has just turned the 2000 mark. This does not include breech cases and cases of incomplete abortion which also had a general anæsthetic. The only general anæsthetic used has been chloroform. I have had none of the major complications mentioned above. In some cases there have been slight complications such as sickness and vomiting. The last case in which I had the latter was in a primipara who was delivered under chloroform anæsthesia about 23.00 hours. She, however, had had a heavy supper which included peaches and cream. That, I concluded, was the cause of her post-anæsthetic vomiting.

METHOD OF USE

Personally, I am of opinion, and it has certainly been my experience, that the amount of chloroform administered by the open method to a woman in labour is not sufficient to cause chloroform poisoning. In the maternity bag I carry a small glass dropper bottle which holds exactly 240 minims (15 ml.) of pure anæsthetic chloroform, and I usually start the anæsthetic myself by dropping some of the chloroform inside the mask. The nurse continues the anæsthetic as directed, and she does not pour it on, but drops it on. I have found that the amount of chloroform used is very often less than 240 minims (15 ml.), and most often it is about 180 minims (10.5 ml.). Some patients, of course, require more: e.g. a nervous patient, or if the case is a difficult forceps one. It takes very little chloroform to anæsthetize a woman who has had a delayed second stage of labour. By then she is usually tired and the anæsthetic takes effect quickly. Recently the nurse called me to a primipara who had a long-delayed second stage due to an occipito-posterior presentation.

In her case the amount of chloroform used was just under 120 minims (8 ml.), and she remained asleep until expression of the placenta.

I now quote from an interesting article in *The Practitioner* of December 1957 (Anderson, 1957):—

'It is quite impracticable to transport heavy apparatus for anæsthesia or analgesia to the patient's home. Drugs should be at hand to relieve the patient of unnecessary suffering. In regard to the later part of labour, nothing facilitates delivery so well as chloroform *à la reine*. The analgesia can be temporarily deepened to permit of episiotomy. For the insertion of silkworm gut sutures in the perineum, a few whiffs of chloroform will be sufficient. Enough has been said to indicate the importance of a bottle of chloroform and a suitable mask'.

ANCILLARY DRUGS

The drugs I carry for use in labour cases are:—

(1) Morphine.—This, when used, is given hypodermically in ¼-grain (16 mg.) doses. This, I am convinced, is beneficial, not only for the relief of pain, but in bringing about the softening and relaxation of a cervix which has been slow in dilating.

(2) Pethidine in tablet form (50 mg.) is given on my instructions early in labour, and repeated when necessary. Given in tablet form I have found it most helpful.

(3) Draught of chloral and potassium bromide B.P.C. is often given early in labour to a nervous primipara. This old mixture certainly has a soothing effect on the nervous type of patient. Chloral alone relieves the early pains of labour without directly hindering the uterine contractions.

(4) Preparations of ergot in case of, or for the prevention of, hæmorrhage. I make it a routine practice to give an intramuscular injection of ergometrine after expression of the placenta and membranes. A few ergot pills are left with the patient with instructions to take them if necessary, and in the case of after-pains I have found aspirin to be quite effective.

GENERAL MEASURES

My usual procedure in domiciliary cases is somewhat as follows. In the antenatal period the patient is seen regularly by the nurse who keeps a record of the blood pressure and urine examinations. In the case of a primipara she is seen by me almost every month, and I have made it a practice to give all expectant mothers a thorough examination three weeks before the date of the expected confinement. The expectant mother is informed that her labour will be made as easy as possible.

It is of great assistance to the practitioner to have in attendance at a confinement a competent nurse; one who does not get flurried or excited if the labour is not going according to the books. We are lucky to have in this village such a nurse. Since the National Health Service started ten years ago she and I have been to many cases in which instrumental delivery under chloroform anæsthesia was done, and so far we have had no major complications in our deliveries or afterwards.

Some years ago I had an unfortunate experience at a case when there was a nurse in attendance. I gave the patient, a primipara, just sufficient chloroform to apply the forceps. Just before starting traction the patient became very rigid, and I asked the nurse to drop on some more chloroform. Instead of doing so she disappeared downstairs, and left me to it. The patient then began to struggle. I was quite unable to remove the forceps owing to the rigidity of the patient, who threw herself to one side of the bed, and the head came through with a great jerk causing a complete tear. I learned later that the nurse had been teaching the patient certain exercises so that her labour would be easy, and she would have her baby without assistance. The exercises had been of little avail, or she had been badly instructed.

SUMMARY

(1) A short account is given of domiciliary midwifery in a country practice, in which chloroform has been the only general anæsthetic used.

(2) When given by the open method—a mask and a drop bottle—chloroform is a safe anæsthetic in labour.

(3) No special apparatus is required for its administration.

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THREE CASES OF PERNICIOUS ANÆMIA

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The relationship between the teaching of medicine and its eventual practice is a problem which continues to trouble all who give thought to this complex question. At University, and later in hospital, diseases and syndromes are described as clear-cut entities whose recognition is necessary for the passing of the requisite examinations. Coming into general practice from this rarified academic atmosphere is a salutary experience. Few illnesses seem to fit into easily labelled compartments and previous laboriously acquired medical knowledge has to be reorientated to changed circumstances.

OCCURRENCE IN PRACTICE

One of the ideas with which I entered upon my medical career was that pernicious anæmia was not a common disease. This notion was quietly fostered during my first five years in rural practice, when on taking over the practice and delving into the hospital records of the several patients receiving cyanocobalamin or liver extract, only two substantiated cases of pernicious anæmia remained. The rest, though protesting, had their therapy discontinued. One patient with a sprue syndrome following resection of a large segment of small bowel, was later found to require cyanocobalamin for the preservation of a normal blood picture, but in no other case did the

drug require to be restarted, nor did any fresh case of pernicious anæmia arise. Pernicious anæmia did, indeed, appear to be a rare disease, but the occurrence of three new cases of the disease within a period of three months quickly changed the picture.

Although the chance occurrence of these three cases in such rapid succession did not mean that pernicious anæmia had suddenly become more common, it does emphasize that one's thinking in these matters has to be properly orientated, or cases well within our diagnostic capabilities will continue to be overlooked. In clinical lectures, pernicious anæmia and its accompanying pathological processes are detailed and its comparative rarity stressed. In the wards and outpatient departments, with their clientele of previously selected cases, pernicious anæmia is often seen and even more often considered. In general practice, on the other hand, anything can happen and it is to stress this point that the following three cases are described, their main interest being that they occurred within a period of three months.

CASE RECORDS

Case No. 1.—A small, stoutly built woman, aged 67, suffered from chronic bronchitis. While away from home in November 1956, she was treated with intramuscular iron for a severe iron-deficiency anæmia and 'nervous exhaustion'. On her return in May of the next year, her hæmoglobin was 86 per cent. and treatment was stopped. In February 1958, she began to complain of extreme tiredness and the hæmoglobin was found to be 45 per cent. Although at that time the blood film showed little abnormality, when she was admitted to hospital a week later, the hæmoglobin had fallen to 25 per cent. and the blood picture was that of a macrocytic anæmia.

The diagnosis was obscured by the preliminary response of the anæmia to iron therapy.

Case No. 2.—A woman, aged 70, was known to have polycystic renal disease and hypertension. In November 1957, she was noted to be pale and to have a hæmoglobin of 60 per cent. A course of oral iron was given to counter this, along with vitamin B tablets for a 'peripheral neuritis'. Six months later the hæmoglobin was 50 per cent. After an extensive course of intramuscular iron, she was still washed out and pale (hæmoglobin 50 per cent.). She was thereupon admitted to hospital where a diagnosis of pernicious anæmia was established. On admission to hospital ten days after the last hæmoglobin estimation of 50 per cent. the hæmoglobin level had fallen to 25 per cent.

The eventual diagnosis was delayed by the presence of concomitant diseases, in both of which a degree of refractory anæmia might be expected.

Case No. 3.—A woman, aged 55, gave a history of episodes of anæmia since puberty. She was also supposed to have had 'angina' as a child. Menstruation had ceased at the age of 40, and when first seen she was having oral iron and 'cytamen' injections. Since no hæmatological investigations had been carried out, treatment was stopped (June 1952), and two months later, the hæmoglobin being 95 per cent. attendance on her ceased. Apart from occasional complaints of palpitation, dizziness and stomal ulcers, she kept well until December 1957, when her hæmoglobin level was found to have fallen to 50 per cent. A month later, despite an intensive course of oral iron, there was no change in this level, so a blood film was taken. This demonstrated a megaloblastic anæmia and further investigation confirmed a diagnosis of pernicious anæmia.

The case demonstrates well the natural remissions which may occur.

COMMENTARY

As has already been noted, several interesting points about the diagnosis and natural history of pernicious anæmia arise from a study of these cases.

(1) *The diagnosis in its early stages is not easy.*—It is in fact a diagnosis, like many others, which probably presents more difficulty to the general practitioner than to the consultant: for one thing, pernicious anæmia occurs mainly in an age-group in which the presence of other co-existing pathological changes becomes more common with advancing years. A developing anæmia may then be easily overlooked, especially when it accompanies a disease in which anæmia is itself a result of the disease process. Also, since the natural history of pernicious anæmia may be one of remission, treatment of the anæmia by iron therapy may give rise to a misleading improvement.

(2) *The eventual onset of an acute anæmia is most dramatic.*—However long the developing anæmia may be overlooked, the occurrence of this acute phase brooks no delay in establishing a diagnosis and starting treatment. Regrettable though it may be, it was at this late stage that the diagnosis was made in two of the cases. Presumably by then, all the existing stores of cyanocobalamin had been completely exhausted. How this complete exhaustion is related to the still reversible process which may give rise to the next point to be described is difficult to say.

(3) *Natural remissions in the disease process may occur.*—The introduction of a truly successful replacement therapy has tended to obscure the fact that the natural history of pernicious anæmia is not one of necessarily continuous downhill progress, but that natural remissions may occur. Because an anæmia improves without the administration of cyanocobalamin, a diagnosis of pernicious anæmia is not necessarily ruled out—a point which previously was not personally appreciated.

The modern young doctor enters general practice with a remarkably wide theoretical knowledge of his subject. He is, however, like the modern writer of sophisticated thrillers, who claimed his heroes were white, his villains were black and his heroines a delicate shade of pink; his knowledge bears as much relation to reality as that author's characters do to real men and women. He has much to learn of his art and just as much to relearn. The gradual gaining of insight into the natural history of disease is one of the rewards of those who seek ever to perfect their knowledge, and it is the general practitioner who is fortunate enough to see health and illness in all its different degrees—and in all its complex forms—not just in the final roles by which diseases are recognized in textbooks, and are apt to appear in hospital practice.

SUMMARY

Three cases of pernicious anæmia are described.

Their study gives rise to several conclusions which are not always associated with textbook descriptions of the disease.

CURRENT THERAPEUTICS

CXXXIX.—PROGESTATIONAL AGENTS AND THEIR CLINICAL USES

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FOR many years, progesterone itself and ethisterone (ethinyltestosterone; anhydrohydroxyprogesterone; pregneninolone) have been the only available progestational agents. Recently, however, the ingenuity of the steroid chemists has led to the introduction of a wide range of new steroids possessing some, though not necessarily all, of the properties of progesterone. Several of these agents are considerably more potent than progesterone itself, whilst some of them appear to possess special properties of their own. All this has led to a reawakening of interest in progestational agents, so that a considerable amount of research has been carried out, mainly in the United States and in Germany. The object of this article is to discuss, from the standpoint of therapeutics, the more important progestogens (fig. 1).

PROGESTERONE

Because it is only feebly active by mouth, progesterone is most commonly administered in oily solution by intramuscular injection, although sometimes it is given in the form of vaginal suppositories. During the luteal phase of the menstrual cycle, the average daily output of progesterone is about 20 mg. and it is therefore unlikely that a lower daily dose could have much therapeutic effect. In pregnancy the daily output is probably between 100 and 400 mg., so that in this condition the therapeutic daily dose must be of the order of at least 100 to 200 mg. It will be noted that this is appreciably higher than that generally used in the past; and it will not always be well tolerated. Indeed, there have been reports (e.g. Wilkins *et al.*, 1958) of the birth of female pseudohermaphrodites of nonadrenal origin to mothers receiving intensive progesterone therapy during pregnancy. Other methods of progesterone administration are in the form of microcrystals, to produce a depot effect, and as implants.

Progesterone microcrystals.—These are administered by intramuscular injection and are considered to exert an effect lasting for three or four weeks; some patients experience quite severe pain at the site of injection—which obviously limits their usefulness.

Progesterone implants.—Progesterone in the form of fused cylindrical pellets has been implanted, mainly in cases of habitual abortion. Unless the pellets are placed deeply in muscle, beneath the deep fascia, by means of a trocar and cannula, they are very likely to extrude. Pellets of 25 and 50 mg. are mostly used; pellets of 100 mg. are seldom retained.

17α-hydroxyprogesterone capronate.—Intramuscular injections of progesterone in oily solution produce only fleeting effects, necessitating frequent, repeated injections. To overcome this, Junkmann (1954) introduced 17α-hydroxyprogesterone capronate as a long-acting ester ('primolut-depot').

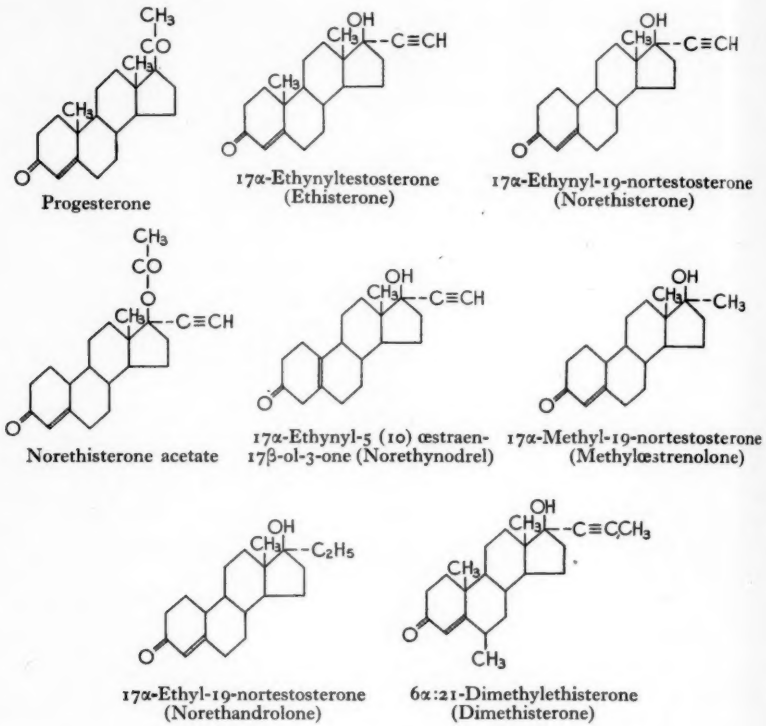

FIG. 1.—The chemical structure of some of the progestogens.

This is available in strengths of 65, 125 and 250 mg. per ml. of oily solution, is well tolerated and exerts an effect lasting for about seven days. Two intramuscular injections, each of 125 mg., seven days apart, can produce a full secretory endometrial response in œstrogen-primed castrate women.

Ethisterone.—This has been widely used as an orally active progestogen for many years but there is no doubt that it is of very low potency, at least as judged by the amount required to produce a full secretory endometrial response in œstrogen-primed castrate women. Thus, whereas a daily intramuscular injection of 20 mg. of progesterone for fourteen days can produce a late secretory endometrium, the daily oral dose of ethisterone required to produce an equivalent response is of the order of 250 to 300 mg. (Wied and

Davis, 1958): i.e. twelve to fifteen times as much. It is doubtful if progesterone orally (or sublingually) is any less potent than ethisterone by the same route (Bickers, 1949). The daily doses of ethisterone commonly administered (5 to 100 mg.) can seldom produce anything approaching a full therapeutic effect.

NEWER PROGESTATIONAL STEROIDS

In recent years, a large number of synthetic steroids, some derivatives of progesterone itself, others nortestosterone derivatives, have undergone testing for progestational activity. Much information on these is collected in the report of a symposium on 'New Steroid Compounds with Progestational Activity' held in 1957 in New York (Rakoff, 1958). From the clinical point of view, interest centres mainly on some of the nortestosterone derivatives which will be discussed further. Mention will also be made of a progestogen, 6α:21-dimethylethisterone (dimethisterone; 'secrosteron'), which is not a norsteroid.

In many of the nortestosterone derivatives progestational activity is marked. In some, for example, 19-nortestosterone, 17α-methyl-19-nortestosterone (methylœstrenolone) and 17α-ethyl-19-nortestosterone (norethandronolone), nitrogen anabolic activity is prominent and to some extent may overshadow progestational potency. These particular steroids also possess androgenic properties; in this respect their potencies are probably rather similar and indeed differ little if any from that of methyltestosterone itself (Saunders and Drill, 1956; Overbeek and de Visser, 1956). On the other hand, 17α-ethynyl-19-nortestosterone (norethisterone; 'primolut N', 'norethindrone') and the Δ 5 (10) isomer, norethynodrel, have œstrogenic rather than androgenic action; for clinical use as progestogens, therefore, these substances would appear to be preferable. All these norsteroids appear to be pituitary inhibitors.

Dimethisterone is a derivative of ethisterone rather than nortestosterone. On animal testing, it has been found to be free from anabolic and androgenic properties. It appears also to be devoid of œstrogenic activity, although this is perhaps a disadvantage for clinical use as a progestogen. The pituitary-inhibiting potency of dimethisterone would seem to be appreciably less than that of the previously mentioned norsteroids.

NORETHISTERONE

This steroid has been studied extensively, particularly in Germany, and several investigators have shown that a total dose of 150 to 200 mg., given over ten days to œstrogen-primed castrate women, or women with secondary amenorrhœa, will produce a good secretory response (Hertz *et al.*, 1956; Ober, 1957; Kaiser, 1957; Pots, 1957; Swyer, 1959a). It is therefore more potent by oral administration than progesterone by daily intramuscular injection. It is well tolerated, and in the usual therapeutic dosage side-effects are rare. With high dosage, however—for example, 30 mg. daily—

nausea, bloating and headache are sometimes experienced. In animal experiments, norethisterone has been found to have a pregnancy-maintaining action (Pincus *et al.*, 1956; Saunders *et al.*, 1957).

Norethisterone œnanthate.—This is another long-acting progestogen, developed by Junkmann (Davis and Wied, 1957). A full secretory endometrial response is obtained following a single injection of 150 mg. The action, however, is so prolonged that withdrawal bleeding may not occur until as much as twenty-eight days after the injection. Ovulation was inhibited by a single injection of 100 mg. on the 6th day of the cycle in all of 10 cases (Wied and Davis, 1958).

Norethisterone acetate.—This is the latest and most potent oral progestogen developed by Junkmann. Pots (1958) found that a total dose of 10 to 40 mg., given over ten days to œstrogen-primed castrate women, produced a full secretory endometrial response. In women with secondary amenorrhœa, Swyer (1959a) found a rather higher total dosage necessary (40 to 80 mg.). Both authors agree that norethisterone acetate is about three times more potent than norethisterone and that it is well tolerated, even in high doses—up to 18 mg. a day.

NORETHYNODREL

This substance differs chemically from norethisterone only in the presence in the first ring of a double bond in the 5 (10) position instead of the 4 (5) position. The original preparations were contaminated by ethynylœstradiol-3-methyl ether and it was found that break-through bleeding was less likely to occur with the œstrogen-contaminated preparation than with pure norethynodrel. In 'enavid', the proportion of ethynylœstradiol-3-methyl ether has been deliberately increased so that each tablet contains 0.15 mg. with 9.85 mg. of norethynodrel. As a result of extensive investigation of 'enavid', mainly in the United States, its properties are well known (see Rakoff, 1958; Conference on 'enovid', 1958).

When administered to normal women in a dose of 10 to 20 mg. daily from the 5th day of the cycle, 'enavid' causes a rapid secretory transformation of the endometrium, but instead of the glands passing into a typical late secretory appearance, they undergo what has been termed 'exhaustion atrophy'. The stroma, on the other hand, is stimulated and a predecidual appearance may be found in biopsies taken on the 19th or 20th day of the cycle. More prolonged treatment produces endometrial appearances similar to those found in mid- or late-pregnancy. On cessation of treatment a withdrawal bleeding usually occurs. If two or three successive cycles of treatment have been given, it is usual for ovulation to be somewhat delayed in the next cycle, so that the first spontaneous period may be a week or ten days late. A proportion of patients are intolerant to 'enavid'; the precise proportion so affected has varied with different observers but on the whole it is probably not less than 20 per cent. Nausea, vomiting, general malaise, dizziness, breast discomfort and headaches are the symptoms most commonly ex-

perienced. In many patients they are mild and soon wear off, especially if the treatment is taken at night, but in others they are sufficiently severe to make treatment impossible.

Like the other norsteroids, 'enavid' appears to have potent pituitary-inhibiting effects. As a consequence, ovulation is prevented and, because of this, it has proved to be a highly effective oral contraceptive (Pincus *et al.*, 1958). In animal experiments, it has not shown pregnancy-maintaining properties.

DIMETHISTERONE

On the basis of the Clauberg test, this steroid is about eleven times more potent than ethisterone. To date, the only published work on its effects in the human is that of Matthew (1959) who found that a total dose of 180 mg. given over twelve days to œstrogen-primed women with secondary amenorrhœa produced secretory changes. Mostly, however, these consisted of subnuclear vacuolation of the gland cells—that is, early changes—and in none of his 10 patients was a late or mid-secretory endometrial picture produced. It is probable therefore that dimethisterone is appreciably less potent, as judged by this criterion, than norethisterone. It is certainly much less potent when administered from the 20th day of a normal cycle with the object of postponing menstruation. Although norethisterone in a dose of 10 to 20 mg. daily given for twenty days from the 20th day of the cycle will regularly prevent the onset of bleeding until after medication has been stopped, doses of dimethisterone up to 40 mg. daily given in the same way have failed to achieve this effect (Swyer, 1959b). In doses of up to 40 mg. daily, dimethisterone seems to be relatively free from side-effects.

CLINICAL USES OF PROGESTOGENS

Threatened and habitual abortion.—Apart from various menstrual disorders, threatened and habitual abortion have hitherto been the main indications for progestogens. It is now fairly clear that the doses commonly employed are unlikely to have had much therapeutic effect and it is therefore not surprising that widespread doubts have been entertained as to whether progesterone is of any real value in these conditions. As we now recognize that, in order to simulate physiological conditions, far higher doses are necessary, and as potent new progestogens are now available, the whole problem ought to receive critical and controlled re-evaluation. On the other hand, it must be remembered that in many cases the cause of abortion is undoubtedly a defect in the ovum and not progesterone insufficiency, whilst in not a few cases of habitual abortion anatomical uterine defects are the responsible factors. It is obvious that progestogens, no matter how potent, cannot help these cases. Caution should therefore be exercised in receiving the apparently encouraging results reported by a number of observers using 17α-hydroxyprogesterone capronate, norethisterone and 'enavid'. Results similar to these have previously been reported with œstro-

gens, vitamins and so forth. The situation is well summed up by Goldzieher's (1958) remark that: 'Bevis (1951), for example, achieved results on a psychotherapeutic basis which do not differ statistically from those obtained by Javert (1954) who used a most complex and restrictive regime, all of which he claims to be essential'.

Progestational insufficiency.—This is a relatively uncommon but quite real cause of infertility and progestogens are logically indicated in its treatment. Ethisterone, in a dose of 60 to 80 mg. daily for ten days from the 15th day of the cycle, will often produce a full secretory response where previously the premenstrual endometrial biopsy had shown inadequate development. Norethisterone, in a dose of 10 to 15 mg. daily, will produce an equally good result. It has often been supposed that continued treatment with progestogen is necessary, should conception occur in these patients, in order to prevent abortion. In my experience, this has not been the case.

Control of dysfunctional uterine bleeding.—Progesterone injections have been used for the treatment of metropathia hæmorrhagica (e.g. Scowen, 1944). By means of these, secretory transformation followed by shedding of the hyperplastic endometrium is obtained and, by regular treatment, regular normal menstrual bleeding can be substituted for the previous prolonged and irregular bleedings. Greenblatt (1947) proposed the use of combined injections of progesterone and testosterone propionate for the control of prolonged bleeding. The precise dosage is unimportant: 25 mg. of each given daily for four days usually arrests the bleeding and is followed a few days later by a progesterone-withdrawal bleeding simulating a normal period.

Evidence has now accumulated that the nortestosterone derivatives may be very useful in the treatment of menorrhagia. As a rule bleeding is promptly controlled by 'enavid' or norethisterone, in a dose of 10 to 20 mg. daily, and a few days after treatment is stopped a withdrawal bleeding occurs. Cyclic treatment for twenty days, from the 5th day of the cycle, given for a few months, is often followed by regular spontaneous menstruation when treatment is stopped. In some cases of regular menorrhagia without organic cause, norethisterone, 10 mg. daily, given from the 15th day of the cycle for ten days, has appreciably reduced the extent and duration of bleeding. Norethisterone acetate, 3 mg. daily, has been equally effective (Swyer, 1959b).

Premenstrual syndrome.—It is commonly supposed that a relative deficiency of progesterone or excess of œstrogen is responsible for the premenstrual psychic disturbances, breast discomfort, migraine, and water retention which some women experience. Although direct evidence for this view is lacking, the use of progesterone in treatment has its enthusiastic advocates (for example, Greene and Dalton, 1953). Intramuscular injections of 25 to 100 mg. thrice weekly during the premenstrual fortnight are effective in some, but by no means all, cases and implants of up to 500 mg. of progesterone have also been used. Ethisterone has in general been disappointing,

but good results have been obtained with norethisterone, 10 to 15 mg. daily for ten days from the 15th day of the cycle. 'Enavid' has also been used successfully but in some patients it aggravates rather than relieves the breast discomfort. In one patient with premenstrual migraine, dimethisterone aggravated the condition. Furthermore, in some patients treated in this way water retention is increased in spite of a decrease in the subjective symptoms. This, however, is usually effectively dealt with by the addition of chlorothiazide, 0.5 g. daily, for four or five days at a time per week.

Dysmenorrhœa.—In primary or essential dysmenorrhœa progesterone appears to play a key role, since if its secretion is prevented by œstrogen administration so as to inhibit ovulation, painless withdrawal bleedings are obtained. On the other hand, progesterone or ethisterone given in the premenstrual phase to these patients usually makes the dysmenorrhœa worse. Nevertheless, norsteroids given from the 5th day of the cycle for twenty days, so as to inhibit ovulation, may also abolish dysmenorrhœa (Rock *et al.*, 1957; Savi and Cigada, 1958). Weinberg (1958) reported a 78 per cent. successful response using 'enavid', 10 mg. daily from the 5th day of the cycle for twenty days, in cases of primary dysmenorrhœa. In secondary dysmenorrhœa, results were appreciably less satisfactory and, where endometriosis was present, this regime generally made the dysmenorrhœa worse —so much so that Weinberg feels such a response to be suggestive of endometriosis where previously it had been unsuspected. It has been observed that if the dose of progestogen is excessive, the resulting withdrawal bleeding may be painful, the high dose of progestogen itself giving rise to dysmenorrhœa. In such patients a lower dose, but one which is still sufficient to inhibit ovulation, may produce a painless period.

Endometriosis.—Although progesterone therapy has been tried in the past, unimpressive results had been obtained and it has generally been considered to be of little value. It has to be borne in mind that the doses used may well have been insufficient to produce any pharmacological effect. With 'enavid', Kistner (1958) has reported successful results in the treatment of endometriosis in a fairly substantial series of patients. His regime is to start with 10 mg. nightly for two weeks, increasing to 20 mg. in the next two weeks, 30 mg. for the next two weeks and thereafter 40 mg. nightly for six to nine months. It will be noted that the treatment is *continuous*. Nausea at the start of therapy was present in 90 per cent. of the patients but it usually disappeared later. In 15 per cent. it was severe—to an extent necessitating discontinuation of treatment in some. It should be emphasized that this regime must be regarded as experimental but it does seem to offer appreciable hope for some patients who otherwise are doomed to persistent pain and discomfort from this distressing disease.

Oral contraception.—The strikingly successful results of the use of 'enavid' as an oral contraceptive in the experiments conducted by Pincus and his colleagues (Pincus *et al.*, 1958) in Puerto Rico and elsewhere are now well

known. It is perhaps doubtful if in its ultimately perfected form 'The Pill' will be a progestogen but certainly the reported results are so encouraging that renewed interest in the problem has been aroused and further advances are now inevitable.

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PRACTICAL DIETETICS

VIII.—DIETS IN TOXÆMIA OF PREGNANCY

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During the past twenty years there have been many conflicting views on the effect of therapeutic diets upon toxæmia of pregnancy; some schools of thought have favoured high-protein diets, and others low-protein or low-sodium diets.

GENERAL WEIGHT CONTROL

At the present time, a great deal of evidence can be found to support the theory that there is an increase in the incidence of toxæmia in overweight women. Following on these findings it has now become the practice at many antenatal clinics to adopt a regime of strict weight control throughout pregnancy. The weight is recorded at each visit, and where there is found to be an increase of 1 pound (450 g.) per week—some obstetricians allow only 12 ounces (340 g.)—a diet not exceeding 1,800 calories, restricted in sodium, is prescribed; this diet is also ordered if the mother is overweight on her first visit. Should these measures prove ineffectual in checking the weight gain, a further reduction in calories is advised, at the same time giving mineral and vitamin supplements to safeguard the intake at the level recommended for pregnancy.

Owing to the perversions of appetite which occur during pregnancy, many mothers find this restriction most irksome and difficult, but with careful and sympathetic instruction they are, in most cases, soon able to adapt themselves to this regime. It is stressed again and again that all essential nutrients must be taken daily, and that excess calories only are curtailed. The restricted sodium content is often the cause of further hardship to the mother, for tasty foods such as ham, bacon, cheese, tinned meat and smoked fish should be taken only occasionally owing to the exceptionally high sodium content resulting from the additional salt used in preserving such foods. She is also asked to refrain from adding salt to her meals at table, but salt may be used sparingly when cooking vegetables, and ordinary bread and butter is allowed at this stage. It is advisable to emphasize at frequent intervals that the diet is only a temporary measure introduced to safeguard the health of both mother and baby, and that after delivery, unless there is medical contraindication, a normal diet can be resumed. A further objection to the diet is the cost which, as a result of the exclusion of made-up dishes, and the inclusion of additional amounts of protein, fresh fruit and vegetables and salads, is somewhat higher than that of a normal diet. These objections are easily overcome when it is pointed out that sweets, chocolates, fancy biscuits, tinned fruits and

alcohol (if taken)—all fairly expensive commodities—are excluded, and should therefore go a long way towards bridging the gap.

1,800 CALORIE DIET FOR PREGNANCY

Low carbohydrate, high protein (90 to 100 g.), restricted salt

FOODS ALLOWED DAILY:—

Whole milk, 2 pints (1.1 litres)
1 large portion of lean meat, not less than 3 ounces (84 g.), cooked weight
1 to 2 eggs
1 large helping of fish (approximately 5 ounces [140 g.]), or offal, poultry or rabbit (not less than 3 ounces [84 g.]), not fried
3 medium slices of wholemeal bread (3 ounces [84 g.])
Butter or margarine, enough to spread thinly on bread (½ ounce [14 g.])
2 portions of fresh fruit
2 potatoes, each the size of an egg (4 ounces [112 g.]), boiled, baked or mashed, *not* roasted or fried
1 medium portion (4 ounces [112 g.]) of carrots, turnips, swedes, leeks, parsnips, or peas
At least two liberal helpings of green vegetables or salad (this may include runner and French beans)

FOODS ALLOWED VERY OCCASIONALLY:—

Bacon, ham, tinned meat, smoked fish, cheese and sausages
Peas—fresh, dried, tinned or frozen
Beans—broad, haricot or baked
Lentils
Bananas, grapes
Sugarless jam or marmalade

FOODS NOT ALLOWED:—

Sweets, chocolate, sugar, glucose
Jam, marmalade, honey, syrup
Cakes, pastry, puddings, ice cream, biscuits, breakfast cereals, porridge
Salad oils, cream, peanut butter (unless replacing daily allowance of butter or margarine)
Thickened sauces, soups and gravies
Salad cream (use vinegar or lemon juice as salad dressing)
Nuts
Dried fruits, fruits tinned or bottled in syrup
Drinking chocolate, cocoa, Horlicks, Ovaltine, etc.
Fruit squashes
Alcohol

Notes:—

A medium helping of breakfast cereal may be taken if the potato allowance for that day is omitted.
Some cottage cheeses flavoured with chives, thyme or sage, and without added salt, are obtainable at the large dairies.
Use salt-free yeast extracts such as Marmite for making gravy and flavouring soup.

DO NOT FORGET TO TAKE EVERY DAY: { ORANGE JUICE (WELFARE) / COD-LIVER OIL *or* VITAMIN TABLETS }

DO NOT ADD SALT TO FOOD AT TABLE

DO NOT EAT FRIED FOOD

SPECIMEN DIET FOR ONE DAY

Breakfast:
Tea, coffee, or milk to drink—*no sugar*
2 eggs, poached, boiled or scrambled
1 medium slice of bread, toasted if desired
Butter or margarine thinly spread on bread or toast

Mid-morning: A drink of tea, coffee, milk or (welfare) orange juice

Luncheon:
A large helping of lean meat
A little thin gravy
2 potatoes, each the size of an egg
A large helping of green vegetables or salad
A medium-sized apple, pear or orange
Tea, coffee or milk to drink

Tea:
Tea to drink
A medium slice of bread
Butter or margarine thinly spread
Salad, or low salt yeast extract spread

Dinner:
Clear soup, if desired—no added salt
A large portion of fish, poultry or offal
A medium helping of root vegetables—other than potatoes
A large helping of green vegetables or salad
A slice of bread or a plain biscuit, with butter or margarine thinly spread
A portion of fresh fruit
Coffee, tea, or milk to drink

Before retiring: A glass of milk

If a reduction in the calorie content is necessary, the substitution of two pints (1.1 litres) of skimmed milk for the two pints of whole milk will bring the intake down to 1,500 calories without causing undue stress and hunger to the mother.

STRICT DIETS

The above diets are those used while concentrating on weight control only. If, in spite of these precautions, there are signs of toxæmia, the patient is admitted to hospital, and the diet often further reduced in calorie content and the sodium intake calculated to a known figure ranging from 500 mg. to 600 mg. (22 mEq. to 26 mEq.) per day, according to the calorie content. The protein content of these diets is kept at a reasonable level by the use of Edosol, a low-sodium synthetic milk powder (Trufood Ltd.), which may be prescribed on E.C. 10 forms, as may Casilan, a low-sodium casein powder (Glaxo Laboratories Ltd.).

The following are examples of the basic diets used in hospital. If it is necessary to lower the sodium content even further, the 15 ounces (420 ml.) of skimmed milk used in the high-protein milk mixture may be replaced by 10 ounces (280 ml.) of Edosol milk with an additional 5 ounces (140 ml.) of water to make up the total to 1 pint (560 ml.). This will reduce the sodium content by 215 mg. (a little over 9 mEq.) in each diet; the calcium content will be reduced by approximately 380 mg. (19 mEq.), and the protein content by 5 g., whilst the calorie content will be increased by nearly 40.

1,200 CALORIE HIGH-PROTEIN, LOW-SODIUM DIET
(For use in cases of toxæmia of pregnancy)

Breakfast: Tea or coffee, no sugar, high-protein milk 1 ounce (28 ml.)
1 Egg, boiled or poached
1½ ounces (42 g.) Low-salt bread, toasted if desired
¼ ounce (7 g.) Unsalted butter or margarine
3 ounces (84 g.) Grapefruit

Mid-morning: 5 ounces (140 ml.) High-protein milk

Dinner: 3 ounces (84 g.) Lean beef
4 ounces (112 g.) Swedes, no salt in cooking
4 ounces (112 g.) Greens, no salt in cooking
Rice pudding made of: ½ ounce (14 g.) rice and
8 ounces (224 ml.) high-protein milk

Tea: Tea, no sugar, high-protein milk (1 ounce [28 ml.])
1 ounce (28 g.) Low-salt bread, toasted if desired
¼ ounce (7 g.) Unsalted butter or margarine
1 ounce (28 g.) Lettuce or ¼ ounce (7 g.) mustard and cress

Supper: 3 ounces (84 g.) White fish, steamed or grilled
3 ounces (84 g.) Tomatoes, grilled
4 ounces (112 g.) Marrow, no salt in cooking
1 ounce (28 g.) Low-salt bread
¼ ounce (7 g.) Unsalted butter or margarine
4 ounces (112 g.) Dessert apple

Bedtime: 5 ounces (140 ml.) High-protein milk

High-protein milk:—
15 ounces (420 ml.) Skimmed milk
5 ounces (140 ml.) Water
1 ounce (28 g.) Casilan

NO SALT ON TRAY

Approximate nutritional content of daily intake:—

Carbohydrate	110 g.
Protein	100 g.
Fat	40 g.
Sodium	506 mg. = 22 mEq.
Calcium	1,225 mg. = 61 mEq.
Iron	13 mg.

1,500 CALORIE HIGH-PROTEIN, LOW-SODIUM DIET
(For use in cases of toxæmia of pregnancy)

Breakfast: Tea or coffee with milk from daily ration, no sugar
1 Egg, boiled or poached
2 ounces (56 g.) Low-salt bread, toasted if desired
½ ounce (14 g.) Unsalted butter or margarine
4 ounces (112 g.) Orange

Mid-morning: 6 ounces (168 ml.) High-protein milk

Dinner: 3 ounces (84 g.) Lean beef
4 ounces (112 g.) Greens, no salt in cooking
4 ounces (112 g.) Potatoes, no salt in cooking
Rice pudding, made of: ½ ounce (14 g.) rice
8 ounces (224 ml.) high-protein milk

Tea: Tea with milk from daily ration, no sugar
1 ounce (28 g.) Low-salt bread, toasted if desired
¼ ounce (7 g.) Unsalted butter or margarine
1 ounce (28 g.) Lettuce or ¼ ounce (7 g.) mustard and cress

Supper: 3 ounces (84 g.) White fish, steamed or grilled
3 ounces (84 g.) Tomatoes, grilled
4 ounces (112 g.) Marrow, no salt in cooking
1½ ounces (42 g.) Low-salt bread
¼ ounce (7 g.) Unsalted butter or margarine
4 ounces (112 g.) Dessert apple

Bedtime: 6 ounces (168 ml.) High-protein milk

High-protein milk:—
15 ounces (420 ml.) Skimmed milk
5 ounces (140 ml.) Water
1 ounce (28 g.) Casilan

Daily ration of skimmed fresh milk = 3 ounces (84 ml.)

NO SALT ON TRAY

Approximate nutritional content of daily intake:—

Carbohydrate	163 g.
Protein	108 g.
Fat	46 g.
Sodium	570 mg. = 25 mEq
Calcium	1,400 mg. = 70 mEq.
Iron	14 mg.

1,800 CALORIE HIGH-PROTEIN, LOW-SODIUM DIET

(For use in cases of toxæmia of pregnancy)

Breakfast: Tea or coffee with milk from daily ration, no sugar
1 Egg, boiled or poached
2 ounces (56 g.) Low-salt bread, toasted if desired
½ ounce (14 g.) Unsalted butter or margarine
4 ounces (112 g.) Orange

Mid-morning: 6 ounces (168 ml.) High-protein milk

Dinner: 3 ounces (84 g.) Lean beef
4 ounces (112 g.) Greens, no salt in cooking
5 ounces (140 g.) Potatoes, no salt in cooking
Rice pudding, made of: ½ ounce (14 g.) rice and
8 ounces (224 ml.) high-protein milk

Tea: Tea with milk from daily ration, no sugar
2 ounces (56 g.) Low-salt bread, toasted if desired
½ ounce (14 g.) Unsalted butter or margarine
1 ounce (28 g.) Lettuce or ¼ ounce (7 g.) mustard and cress

Supper: 3 ounces (84 g.) White fish, steamed or grilled
3 ounces (84 g.) Tomatoes, grilled
4 ounces (112 g.) Marrow, no salt in cooking
2 ounces (56 g.) Low-salt bread
½ ounce (14 g.) Unsalted butter or margarine
4 ounces (112 g.) Dessert apple

Bedtime: 6 ounces (168 ml.) High-protein milk

High-protein milk:—

15 ounces (420 ml.) Skimmed milk
5 ounces (140 ml.) Water
1 ounce (28 g.) Casilan

Daily ration of whole fresh milk = 5 ounces (140 ml.)

Approximate nutritional content of daily intake:—

Carbohydrate	193 g.
Protein	113 g.
Fat	64 g.
Sodium	598 mg. = 26 mEq.
Calcium	1,500 mg. = 75 mEq.
Iron	15 mg.

NO SALT ON TRAY

SODIUM EXCHANGES

In order to keep the sodium content at this low level, food exchanges for the basic diets must be selected with care, as the amount of sodium which occurs naturally in our basic foods varies considerably. When using these exchanges care should be taken to keep the protein intake adequate.

Examples of approximate sodium exchanges for some of the items of food in these diets are given below:—

Foods containing approximately the same amount of sodium as an average-sized egg:—

Cod, grilled	2½ ounces	(70 g.)	Liver (calves'), grilled	2 ounces	(56 g.)
Cod roe, grilled	2 ounces	(56 g.)	Salmon, fresh, steamed, with bone	3 ounces	(84 g.)
Herring, baked in vinegar, with bone	4½ ounces	(126 g.)	Tongue (sheep's), unsalted	3 ounces	(84 g.)
Kidney (sheep's), grilled	1 ounce	(28 g.)	Trout, steamed, with bone	4½ ounces	(126 g.)

Foods containing approximately the same amount of sodium as 3 ounces (84 g.) of lean beef:—

Chicken, roast	2½ ounces	(70 g.)	Rabbit, stewed	6½ ounces	(182 g.)
Chicken, boiled	2½ ounces	(70 g.)	Sweetbreads, stewed	3 ounces	(84 g.)
Duck, roast	1 ounce	(28 g.)	Tongue, stewed	2¾ ounces	(77 g.)
Hare, roast	4 ounces	(112 g.)	Tripe, stewed	3 ounces	(84 g.)
Kidney (ox), stewed	1¼ ounces	(35 g.)	Turkey, roast, with bone	2¾ ounces	(77 g.)
Liver, raw	2½ ounces	(70 g.)	Veal, roast	2¼ ounces	(63 g.)
Mutton, lean, roast	3 ounces	(84 g.)			
Pork, lean, roast	3 ounces	(84 g.)			

Foods containing approximately the same amount of sodium as 3 ounces (84 g.) of white fish (without bone):—

Beef, lean, roast	4½ ounces	(126 g.)	Mutton leg, boiled	5 ounces	(140 g.)
Brain, calves', boiled	2 ounces	(56 g.)	Pigeon, boiled	4½ ounces	(126 g.)
Cheese, cheddar	½ ounce	(14 g.)	Pigeon, roast	3 ounces	(84 g.)
Cheese, cream	3 ounces	(84 g.)	Pork chop, grilled, lean only	3 ounces	(84 g.)
Chicken, boiled	3 ounces	(84 g.)	Salmon, steamed, fresh, with bones	3½ ounces	(98 g.)
Hare, roast	6 ounces	(168 g.)	Sweetbreads, stewed	4½ ounces	(126 g.)
Heart, sheep's roast	2 ounces	(56 g.)			
Liver, raw	3 ounces	(84 g.)			
Mutton chop, grilled, lean only	2½ ounces	(70 g.)			

Foods containing approximately the same amount of sodium as 3 *ounces* (84 *g.*) *of grapefruit:—*

Apples, dessert	2 ounces	(56 g.)	Damsons, raw	2 ounces	(56 g.)
Apricots, fresh	A good helping		Figs, green	2½ ounces	(70 g.)
Banana	4 ounces	(112 g.)	Grapes, white	3 ounces	(84 g.)
Blackcurrants, stewed, without sugar	2½ ounces	(70 g.)	Greengages, raw	3 ounces	(84 g.)
			Peaches, fresh	1½ ounces	(42 g.)

Foods containing approximately the same amount of sodium as 4 *ounces* (112 *g.*) *of orange or dessert apple:—*

Cherries, eating	4 ounces	(112 g.)	Melon, cantaloupe, without skin	1 ounce	(28 g.)
Currants, black, raw	4 ounces	(112 g.)	Nectarines, with stone	1¼ ounces	(35 g.)
Damsons, raw	5 ounces	(140 g.)	Peaches, fresh	4 ounces	(112 g.)
Figs, green	6 ounces	(168 g.)	Pears, dessert	4 ounces	(112 g.)
Gooseberries, ripe	10 ounces	(280 g.)	Pineapple, fresh	6 ounces	(168 g.)
Grapes, black	6 ounces	(168 g.)	Plums, dessert	6 ounces	(168 g.)
Grapefruit, as eaten	8 ounces	(224 g.)	Raspberries, raw	4½ ounces	(126 g.)
Greengages, raw	8 ounces	(224 g.)	Rhubarb, raw	5 ounces	(140 g.)
Lemon juice, undiluted	8 ounces	(224 g.)	Strawberries	8 ounces	(224 g.)
Loganberries, raw	4½ ounces	(126 g.)	Tangerines	5 ounces	(140 g.)
Medlars	2 ounces	(56 g.)			

Foods containing approximately the same amount of sodium as 3 *ounces* (84 *g.*) *of grilled tomatoes:—*

Cucumber, raw	3 ounces	(84 g.)	Lettuce, raw	2½ ounces	(70 g.)
Endive, raw	1 ounce	(28 g.)			
Spring onions, raw	¾ ounce	(21 g.)	*Note:*—Watercress, radishes and celery all have a high sodium content.		
Mustard and cress, raw	½ ounce	(14 g.)			

Foods containing approximately the same amount of sodium as 4 *ounces* (112 *g.*) *of swedes:—*

Beans, broad, boiled	3 ounces	(84 g.)	Cauliflower, boiled	5 ounces	(140 g.)
Beans, French ,,	16 ounces	(448 g.)	Leeks ,,	9 ounces	(252 g.)
Beans, haricot ,,	3 ounces	(84 g.)	Onions ,,	8½ ounces	(238 g.)
Beans, runner ,,	18 ounces	(504 g.)	Parsnips ,,	13 ounces	(364 g.)
Beetroot ,,	under 1 ounce	(28 g.)	Peas, fresh ,,	12 ounces	(336 g.)
			Sea kale ,,	15 ounces	(420 g.)
Brussels sprouts ,,	7½ ounces	(210 g.)	Spinach ,,	½ ounce	(14 g.)
Cabbage, savoy ,,	7 ounces	(196 g.)	Spring greens ,,	6 ounces	(168 g.)
Cabbage, spring ,,	4½ ounces	(126 g.)	Turnips ,,	2 ounces	(56 g.)
Cabbage, winter ,,	4½ ounces	(126 g.)			
Carrots, old ,,	1½ ounces	(42 g.)	*Note:*—Old carrots, and spinach have a high sodium content.		
Carrots, young ,,	2½ ounces	(70 g.)			

Foods containing approximately the same amount of sodium as 4 *ounces* (112 *g.*) *of marrow:—*

Asparagus, boiled	4 ounces	(112 g.)	Onions, boiled	¾ ounce	(21 g.)
Beans, French ,,	1 ounce	(28 g.)	Sea kale ,,	1 ounce	(28 g.)
Beans, runner ,,	1½ ounces	(42 g.)	Turnip tops ,,	¾ ounce	(21 g.)
Leeks ,,	1½ ounces	(42 g.)			

REVISION CORNER

THE TREATMENT OF CONGENITAL PYLORIC STENOSIS

THERE must be few diseases in childhood in which a simple operation, such as that devised by Ramstedt, in 1911, has revolutionized treatment to the same extent. Before this, the mortality was as high as 80 per cent.; with the new method the death rate soon fell dramatically to 20 per cent. Since then, advancing skill in pædiatric surgery, realization of the problems connected with dehydration and electrolyte disturbance, and prevention of postoperative gastro-intestinal infection have reduced the mortality to almost nil. Wood and Smellie, in 1951, gave a figure of 1.5 per cent. in an analysis of 320 cases, and there must be many hospitals which can now produce an equally good record.

MEDICAL TREATMENT

Is there then any place for medical treatment? This still seems to find favour in some pædiatric centres, particularly in Sweden. It is difficult to be sure that the condition they are treating may not in fact include certain cases of pylorospasm, as outside Great Britain palpation of a tumour is not considered an essential hallmark of the condition. There is little doubt that surgery offers the best means towards rapid recovery, provided the operation is in expert hands. There are, however, degrees of severity in this condition, and if the vomiting is not serious and weight continues to increase, there is some justification for adopting medical measures. The same applies to infants who have a late onset of their disorder, bearing in mind that at about three months of age spontaneous improvement tends to occur.

Medical treatment consists of gastric lavage twice a day until the fluid washed out of the stomach becomes clear. Normal saline should always be used in order to combat the alkalosis which has usually resulted from continuous vomiting. Combined with this, atropine methonitrate is given twenty minutes before each feed, either as a lamella, containing $\frac{1}{750}$ grain (0.09 mg.) ('pylostropin'), or in a dosage of 5 ml. of a 1/10,000 freshly prepared aqueous solution ('eumydrin'). Thickening the feeds has also been recommended, but pyloric obstruction is surely a contraindication to this.

SURGERY

As already indicated, surgery is the treatment of choice in most cases. If a surgeon well versed in the technique is not available, medical measures may well be preferable but, should these not soon prove successful, the infant must be transferred to an appropriate centre, where surgical facilities exist.

PREOPERATIVE PREPARATION

Preoperative preparation is most important. Early recognition of the condition, by observing projectile vomiting and gastric peristalsis, and by palpation of a tumour during a feed, has certainly reduced the number of infants brought to hospital in a seriously dehydrated condition. But diagnostic difficulties can arise, which may finally be solved radiologically, or by discovering a residue three to four hours after a feed on washing out the stomach.

A rough estimate of the dehydration should be made. If it is only moderate, 10 to 15 ounces (300 to 450 ml.) of half-strength normal saline may be given subcutaneously. The giving set is connected to a Y-tube so that fluid is run in through two needles simultaneously into each thigh. Absorption is aided by the injection, early in the procedure, of 1 mg. of 'hyalase' into the tube on each side close to the needle. Severe dehydration requires intravenous fluid, a stab scalp-vein technique being the best method. If possible, estimation of the electrolytes in the blood should be made (sodium, chloride, and bicarbonate). Alkalosis is commonly discovered, and this must be rectified by half-strength normal saline, or even a few ounces of full-strength normal saline, as a preliminary measure. Thereafter rehydration should be continued with half-strength normal saline, or half-strength Hartmann's solution and 2.5 per cent. dextrose, and completed in twenty-four hours by the time the operation takes place.

Shortly before the operation gastric lavage is undertaken in order to empty the stomach of milk curds and mucus.

OPERATION AND ANÆSTHESIA

Operation is best carried out under local anæsthesia, using about 10 to 15 ml. of half per cent. lignocaine. Premedication with chloral hydrate is useful (1 grain for every 3 pounds (45 mg. per kg.) of the baby's weight) and, if the infant is restless during the operation, a dummy dipped in glycerin or brandy is generally a comfort. Some centres work with full-scale modern anæsthesia, but for this simple operation it hardly seems necessary. If a general anæsthetic is preferred, gas and oxygen with a relaxant is quite adequate.

This is not the place for a detailed account of the surgical technique, but it might be useful to emphasize one or two ways in which the operation may go wrong. The hypertrophied pyloric muscle merges very closely into the thin-walled duodenum. Well aware of this, the surgeon may falter in his pyloric incision and fail to cut through the entire length of the circular muscular fibres and so not completely relieve the condition. Alternatively, he may go too far and with a bold incision find that he has made a hole in the duodenum. This is not the major tragedy it first appears. Squeezing the stomach will demonstrate the site of the hole, and this is a wise precaution at this stage of the operation in every case. The breech is repaired

by one stitch of atraumatic catgut, incorporating a strip of omentum. By this means a further leak will be prevented, with the danger of subsequent peritonitis. As an additional precaution intramuscular penicillin and streptomycin can be given, and with this cover for the next few days it is usually unnecessary to delay feeding.

Infants with pyloric stenosis are often wasted and their skin does not possess good healing properties. The abdominal wound is therefore apt to break down. Great care should be taken to ensure that the omentum is tucked well away before the peritoneum and posterior sheath of the rectus are carefully sewn up. Then the anterior sheath is stitched together in the next layer and finally the skin, making certain that the edges are carefully opposed.

POSTOPERATIVE CARE

Feeding is begun four hours after the operation with 5 per cent. dextrose hourly in teaspoonful amounts. After four such feeds diluted half-cream milk feeds should be introduced, still at hourly intervals, gradually increasing the quantity and strength. After six hours' rest during the night, the same scheme is followed at two-hourly intervals. In this way the infant should have returned to his normal feeding routine forty-eight hours after the operation.

A similar procedure is adopted in a breast-fed baby, the milk being expressed during the first twenty-four hours. After that the infant can be put to the breast two-hourly for short periods of three or four minutes at first. From then onwards a longer time is permitted, and by the third day after the operation normal breast feeds should have been reached.

Vomiting usually ceases following a successful Ramstedt's operation, but occasionally it may continue spasmodically for a few days. It is probably the result of traumatic œdema of the pylorus and is well controlled by a short course of 'eumydrin'. The surgeon's anxiety over an 'incomplete' resection is usually unfounded and the temptation to carry out further surgery should be resisted. Generally in these circumstances the baby will begin to thrive and gain weight in a short while. It is rarely necessary to resort to gastric lavage.

If the operation has been adequately performed, peristalsis should cease forthwith, but a tumour may remain palpable for months or even several years. Meanwhile the baby makes great strides and usually grows more rapidly in length and weight than an average infant.

Infection was the greatest feared complication in the past and gastro-enteritis took its toll, but with the modern system of cubicles and stricter nursing precautions this danger has been overcome. Nevertheless, the infant should be discharged from hospital as soon as possible—at the end of a week or even earlier—and brought back for removal of stitches on the tenth day.

Finally it must be realized that pyloric stenosis and hiatus hernia are sometimes associated. Radiological investigations may become necessary to exclude the latter, if vomiting continues postoperatively and has not responded to the treatment suggested.

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THE MANAGEMENT OF POLYCYTHÆMIA

THE patient with polycythæmia comes to his doctor because of four main symptoms. (1) The colour of his face and lips is changing to a dusky purple and his conjunctivæ are suffused; this leads to comments about blood pressure and excessive alcohol. (2) Headaches increasing in severity. (3) Peripheral circulatory symptoms which may be limited to undue aching of the limbs after exercise or may be due to actual thromboses. (4) Cardiac symptoms such as dyspnœa on exertion. The patient is usually aged 50 or more and men are affected twice as often as women, but the condition does occur in younger persons, even in children. To be significant a blood count should show a red cell count of over 6.5 million per c.mm. and hæmoglobin more than 18 g./100 ml. (120 per cent.).

PRIMARY OR SECONDARY

The next point to settle is whether the polycythæmia is primary or secondary, because the management methods to be described apply only to the primary disease. Polycythæmia vera is a primary blood disease due to over-production of red cells by the bone marrow. The blood count nearly always shows an increased white cell count as well: figures of 20,000 per c.mm. are common and a few immature granulocytes are often present. On clinical examination a palpably enlarged spleen is always found sooner or later and, in fact, failure to palpate the spleen practically rules out primary polycythæmia. The secondary forms of polycythæmia are due to cardiac or pulmonary disease, or to decreased plasma volume without any change in the red-cell mass, as in the 'stress polycythæmia' of Lawrence and Berlin, or in the polycythæmia sometimes associated with hypertension. The management of these secondary forms is that of the disease responsible.

The object of treatment in polycythæmia vera is to reduce the red-cell mass so as to restore a more normal proportion of cell and plasma volume, and so to reduce the viscosity of the blood and the sluggish peripheral circulation which is responsible for the dangerous thrombotic complications. This used to be accomplished by using drugs such as

phenylhydrazine that destroyed red cells, but this group of drugs is not now used; instead we have drugs that act on the bone marrow which are, in fact, more easily controlled.

RADIOACTIVE PHOSPHORUS

Radioactive phosphorus (P^{32}) has now been used for twenty years and gives very good results. It is given in the form of isotonic sodium phosphate solution which is preferably administered intravenously. The dose varies from 4 to 7 millicuries according to the severity of the disease and the size of the patient; the whole dose is usually given in a single injection. After the injection full blood counts, including platelet counts, are carried out at regular intervals of two to four weeks, and the maximum effect is obtained after three to four months. Most patients respond satisfactorily with relief of symptoms, reduction of the red cell count and hæmoglobin to near normal levels, and shrinkage of the enlarged spleen which becomes no longer palpable. Some patients need a second dose of 2 to 3 millicuries four months after the first dose, and some do not respond at all and have to be given other forms of treatment. But in successful cases it is at least six months, and may be as much as five years, before further treatment is needed.

A not unexpected difficulty which has arisen with radioactive phosphorus is that the proportion of cases terminating in acute leukæmia, usually myeloblastic, has increased and, although the direct connexion is not proved, the association is close enough to be disturbing. For this reason P^{32} treatment is not often used for the younger patients, say under 55 years of age; other methods of control are tried first. Another practical difficulty is that it is usually considered necessary to admit the patient to hospital for treatment because the urine contains appreciable amounts of radioactive material for up to four days after an intravenous dose.

NITROGEN MUSTARDS

These drugs give good control of polycythæmia vera; two types have been used. (1) Mustine B.P., or 'trillekamin', 6 mg., given in a running saline drip. Two or three consecutive doses are needed according to the severity of the case. The disadvantage of these drugs is that in some patients they cause unpleasant vomiting two hours after the injection. (2) Thiotepa (triethylene thiophosphoramide) can be given intramuscularly: four doses, each of 25 mg. in 2.5 ml. of saline, are given on alternate days. This rarely causes reactions, but it is less effective than the nitrogen mustards. Thiotepa, however, is very useful for mild cases and for maintenance after initial treatment with the mustine or 'trillekamin'. (3) Tretamine (triethylene melamine) is a nitrogen mustard type of compound that can be given orally, but its action has proved to be irregular and it is not now recommended. No other oral nitrogen mustard compound for polycythæmia is yet available.

VENESECTION

Repeated venesection is a useful auxiliary method of relieving symptoms in polycythæmia and preventing their recurrence when the blood count begins to rise again as the effect of specific treatment wears off. Used at the beginning of treatment it gives rapid symptomatic relief, and later on it prolongs the intervals between the courses of radiophosphorus or mustards. Usually one pint (550 ml.) of blood is withdrawn at a time and this can be done at intervals of one to four weeks, or even longer as symptoms and the blood count indicate. Repeated venesection often causes more lowering of the hæmoglobin level than the red cell count, so that a low colour-index blood picture appears. When this happens, decision about further venesection should be based on the hæmoglobin and not on the red cell count. Another point to note here is that the new automatic blood-counting machines, being more accurate, tend to give higher red cell counts in polycythæmia than we have been used to with ordinary counting and some allowance must be made for this.

The blood drawn from polycythæmia patients should not be wasted. All the evidence points to the conclusion that the red blood-cells are normal and capable of normal survival, and the blood should be passed to the hospital blood bank for use.

Thromboses in peripheral blood vessels can be troublesome in polycythæmia vera and the patients should be given anticoagulant treatment, provided the platelet count has not been depressed below 40,000 per c.mm. by specific treatment.

PROGNOSIS

With such management most patients with polycythæmia vera can be successfully controlled and can lead an active normal life. The aim should be to give the minimum of drugs that depresses the bone marrow.

When deciding on the frequency of treatment the patient's clinical condition should be taken into account as well as the state of his blood. Regular blood examinations at intervals of about three months should be carried out to watch for relapses and also so that any change in the blood picture can be detected. The changes possible are that a leukæmia may appear or that a myelofibrosis may develop. The treatment of both these conditions is different from that used in the management of polycythæmia; hence the need for vigilance. But by and large the prognosis of polycythæmia vera is good and the prospect for active survival is over ten years.

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Consultant Physician, Manchester Royal Infirmary;
Lecturer in Hæmatology, University of Manchester.

NOTES AND QUERIES

Definition of Hypertension

QUERY.—How would you define 'hypertension'? I have a female patient, 42 years of age, who is perfectly fit and well, and does not complain of headaches. She is not obese and has always enjoyed good health. During an examination for an insurance policy I found the blood pressure to be 180/110 mm. Hg. This was checked, re-checked and an hour later was still 170/105 mm. Hg. The urine was clear and there were no adverse clinical findings. The following day I returned to find the blood pressure 170/105 mm. Hg. Is treatment indicated? What is the prognosis?

REPLY.—The definition of hypertension is no simple matter. It should be realized that measurements of blood pressure, in common with measurements of any other biological characteristic, show a wide variation from one individual to the next. For example, in a given population there is a wide range of height, with a small number of very tall and very short individuals, a larger number who differ slightly one way or the other from the average and a high peak number who are of 'average height'. So when measurements of blood pressure are made there is a wide range from very low to very high values each in a few individuals, with a predominance of readings around the accepted 'normal' value. The difficulty is definition as to when a rather high reading is to be regarded as coming into the high normal category or as definitely abnormal.

Figures for the upper limit of normal pressure vary from one authority to the next. The commonly accepted value is 140/90 mm. Hg; Wood quotes 145/90; Evans regards somewhat higher pressures as normal. My practice is to regard a basal reading of 140/90 as the border line.

The pressures quoted for this patient (170/105 mm. Hg) are to be classed as abnormally high. This is provided, of course, that the readings were taken under approximately basal conditions with the patient relaxed, in a pleasant warm room and recumbent for some ten to fifteen minutes before the reading was made.

As regards management, the first step is to exclude underlying disease, particularly renal disease or coarctation of the aorta. This having been done, no treatment is indicated and the patient should not be informed of the pressure reading. The greatest risk for this patient is the development of a blood-pressure phobia.

The prognosis in a case of mild hypertension in a woman around the menopause, as here, is excellent. It is generally recognized that women of middle age can sustain even a severe hypertension for many years without disability and the prognosis in that sex and age-group is much better than in men.

PROFESSOR IAN G. W. HILL, C.B.E., T.D., M.B., F.R.C.P.ED.

Puerperal Depression

QUERY.—A woman of normally cheerful disposition has had two children, now aged five and three. Each time she had puerperal depression, although the second time this only started a few weeks after delivery, when she had additional domestic strain. She now expects her third baby. In these circumstances (a) is a recurrence of depression likely?, and (b) is this aggravated by breast-feeding, which she did each time previously and enjoyed? She herself is anxious to feed the baby for at least a month, unless there are strong contraindications.

REPLY.—In the circumstances outlined, I do not think one can regard the recurrence of depression as unlikely. On the other hand, it seems that the attack which followed the second labour was less severe than the attack following the first one and I would therefore feel that, on this occasion, if other stresses can be avoided or reduced to a minimum, there is a good chance that no such trouble will develop. As regards (b), I think that breast feeding would be an advantage rather than otherwise—certainly unless, or until, any sign of a recurrence of the depression develops.

ALAN BREWS, M.D., M.S., F.R.C.S., F.R.C.O.G.

Antibiotics and Chronic Sinusitis

QUERY (from a reader in Rhodesia).—I came across a report recently to the effect that 'sigmamycin' had a 'remarkable effect against chronic sinusitis'. Has this been confirmed elsewhere?

REPLY.—The bald truth is that no antibiotic can ever 'cure' long-standing chronic sinus infection. If chronic sinus infection flares up and becomes again acute, then any suitable antibiotic is likely to be of great value. Even in this acute stage the most effective antibiotic will be the one proved (in the laboratory) most lethal to the predominating organisms.

W. I. DAGGETT, M.B., F.R.C.S.

Ocular Albinism

QUERY.—I have been consulted regarding the prognosis in the case of a male child aged 18 months. He is a fair haired, blue-eyed, healthy-looking child, who has lateral nystagmus of pendular character. He is tolerant to sunlight

though screwing up his eyes on bright days. He developed a tan last summer. Playing with toys he seems to have normal vision and is able to recognize animal shapes in a picture book. A diagnosis of partial albinism was made some time ago, and a poor prognosis regarding visual acuity was given at this time. It would seem therefore that the diagnosis is partial albinism with nystagmus, without associated head movements. This, I believe, is a sex-linked recessive character. There is no family history of albinism.

Could you please answer the following questions:—

(1) Can albinism occur other than as a genetic inherited mechanism?

(2) May the mutant gene arise spontaneously? Both parents are of British stock, but born and nurtured in the hill country of Northern India.

(3) May the visual acuity be determined by any method at this age?

(4) What may be done to improve visual acuity? May melanin formation and deposition in the retina be stimulated by the use of any therapeutic agent such as methoxypsoralen?

(5) What advice regarding future family planning should be given to the parents? It is their ambition to have five boys.

REPLY.—It is assumed that by partial albinism ocular albinism is meant as opposed to generalized albinism. Nystagmus is a feature of ocular albinism, but nystagmus by itself is not evidence of the presence of ocular albinism. From the account given it is an open question whether this child does indeed suffer from ocular albinism. Clearly the boy is not suffering from spasmus mutans which is an environmental affection, transient in character. There are two distinct genetic problems involved in this question. If the child is suffering from congenital nystagmus, the condition is not necessarily genetic in origin. The hereditary cases conform to two patterns, recessive sex-linkage and irregular dominance, though there is good evidence that the cases regarded as irregularly dominant are probably X-chromosomal and not autosomal, and that the dominant X-chromosomal gene is allelic to the recessive gene. The significant thing is that an obvious family history is not readily available in many cases. This may well be the case with this particular child. On the assumption that this boy suffers from ocular albinism—which is an intermediate rather than a recessive sex-linked affection—the lack of a family history is again not particularly uncommon.

The prognosis in the case of this child is difficult to assess, but it is worth remembering that nystagmus by itself need not necessarily affect vision markedly. For that matter, even ocular albinism is compatible with relatively good sight. Altogether there is no need to be unduly perturbed.

As regards the specific questions, these can now be answered briefly:—

(1) Yes.

(2) Yes, but it is not necessary to postulate this.

(3) Yes, but the results are not very accurate. Any simple common-sense procedure will do as well as the more elaborate methods that have been described.

(4) The first question may not arise. If there is ocular albinism, nothing can be done to stimulate pigment formation, and there is no reason to assume that pigment formation by itself would help; there is likely to be an underlying cytological defect.

(5) Assuming that we are dealing with a genetic abnormality, the chances of other children being affected depend upon whether the condition is sex-linked or irregularly dominant. If sex-linked, 50% of boys will be affected, and none of the girls—though 50% would be carriers; if irregularly dominant, it is difficult to give mathematical ratios, but presumably less than 50% would be affected and there would not be a heavy male excess.

Nothing is said as to whether the parents are consanguineous. Consanguinity is not a factor in sex-linkage or irregular dominance, but would arise in generalized albinism of a mild type, as generalized albinism is inherited in a recessive autosomal manner. It is unlikely that this particular case falls in this category.

PROFESSOR ARNOLD SORSBY, M.D., F.R.C.S.

Polycystic Disease of the Kidney

QUERY.—A woman patient recently lost her six-month-old baby (her second child) with polycystic disease. Her first child was born prematurely and subsequently died with symptoms consistent with polycystic disease. Assuming this diagnosis in both cases, what are the chances of the mother having a further child with this condition?

REPLY.—Polycystic disease of the kidney, present in adult life, is known to be due in most instances to a dominant mutant gene. But I know of no large series of families of children with infantile polycystic disease of the kidney which is genetically distinct on which to base an estimate of the risks. It is unusual for a mother to have two children with this condition but, assuming that in this case both children were affected in the same way, the risks are probably somewhere between 1 in 4 and 1 in 20 of the next child being affected.

C. O. CARTER, B.M., M.R.C.P.

Arthrodesis of the Hip and Shooting

QUERY.—I have a male patient, aged about 63 years, for whom arthrodesis of the hip is proposed. He is a keen game shot. Can you inform me how much the operation will interfere with his shooting should it be performed?

REPLY.—The patient will probably have to get to the site of the shoot in a Land Rover. He will not be able to climb over gates. He will be able to put up a reasonable performance of rough shooting walking through roots. He will be able to shoot in a butt although he had better be at the end of the line. He may not be much good at high driven birds because he will not be able to get his gun back over his shoulder quick enough. He might be able to shoot grouse from a butt and slaughter duck from the duck punt provided that there is easy access for getting into the punt, and that he can swim.

All this depends on the arthrodesis being successful and in the optimum position.

RONALD FURLONG, M.B., F.R.C.S.

Senile Purpura

QUERY.—Some old people in the 70 to 80 age-group begin to have senile ecchymosis about the hands and forearms. Is vitamin K or other treatment good for this?

REPLY.—The research of the Leeds school, using the electron microscope, has shown that so-called 'senile purpura' is associated with degenerative changes in the connective tissues at the sites mentioned. When such changes take place, the veins lack support and are easily damaged by minor trauma. This causes effusion of blood from the vessels, clinically manifested as ecchymoses.

So far no treatment has been found to prevent these changes.

TREVOR H. HOWELL, F.R.C.P.ED.

Pony Riding and Poliomyelitis

DR. JOAN BISHOP writes:—Pony riding as a form of physiotherapy for children with poliomyelitis and similar disabilities has been found of considerable value, especially on the Continent. Not only do the children benefit physically, but they also gain much psychological help from this pastime. Many children who are unable to run about can compete with normal children if mounted on a quiet pony.

A weekly class is being held for these handicapped children at Bookham in Surrey. The charge is dependent upon their parents' financial means, the lessons being free to those children who could not otherwise afford them. Any doctor or parent who is interested should contact the writer or Mrs. J. Chippendale, 'Kenilworth', Bookham, Surrey. Tel. Bookham 364.

Eggshell for Anæmia in Children

DR. C. PIJPER (Natal, South Africa) writes:—'I read with much interest the report in the May issue of *The Practitioner* (p. 657) that "Hungarian workers have found egg-shell of value in the treatment of anæmia in children". This belief is by no means confined to Hungary. It is, for instance, a common belief among the rural population in parts of The Netherlands'.

PRACTICAL NOTES

Trimeprazine and Pruritus

IN both adults and children, trimeprazine would seem to have a place in the relief of pruritus, according to T. E. Anderson and D. Chalmers (*British Journal of Dermatology*, June 1959, **71**, 214) as a result of a trial involving 102 adults with a variety of dermatological conditions associated with itching, and 53 children with itching associated with infantile eczema or juvenile atopic dermatitis. Trimeprazine is a phenothiazine derivative which can be regarded pharmacologically as being intermediate between promethazine and chlorpromazine. The dosage used for the adults was 10 mg. four times a day. In the children the daily dosage ranged from 10.8 to 28.8 mg., in divided doses, according to age, weight and severity of itching, given in the form of a syrup containing 7.2 mg. per 4 ml. Of the adults in the series, 83 received trimeprazine and the remainder an inert tablet. The statistician's report on the results of the trial states: 'The proportions showing some or a marked improvement were greater in the treated than in the control group. The probability that a consistent advantage of the size obtained, or larger, would have occurred by chance in the trial, if there was no true difference between the effects of the drug and the inert substance, is less than 0.001%, i.e. one in a hundred thousand'. Typical of the results is that in atopic dermatitis, eczema and neurodermatitis the drug was beneficial in all but two out of a total of 54 cases. Of the 53 children in the series, all of whom received trimeprazine, all but five showed some benefit. Side-effects were minimal.

Humycin in Salmonellosis

HUMYCIN, or humatin, is a streptomyces antibiotic which has been shown to be active against *Salmonella typhimurium* infections in mice. It is nephrotoxic when administered parenterally, but it is not absorbed from the gastro-intestinal tract when given orally. W. F. Twining McMath and K. K. Hussain (*Public Health*, June 1959, **73**, 328) have investigated its action in a series of 38 patients with food poisoning due to *Salmonella typhimurium*. In every case the diagnosis was confirmed bacteriologically, and the criterion of cure was six consecutive negative stool cultures over a period of two weeks, starting three days after the cessation of a five-day course of treatment. The daily dose ranged from 40 to 75 mg. per pound (88 to 165 mg. per kg.) body weight, given in divided doses by mouth every six hours. A 'suitable amount of vitamin B complex was given to all patients as routine'. Among the 38 cases treated with humycin there were seven failures, compared with 40 failures among 67 patients treated with antibiotics other than humycin. All but one of the failures occurred among the patients who were given less than 88 mg. per kg. daily. Among eight patients treated with a combination of humycin and oral streptomycin (1 g. daily) there were no failures. No side-effects were encountered with humycin. Neither was there any evidence of salmonellæ developing resistance to the antibiotic.

Ergotamine and Migraine

IN the opinion of A. P. Friedman and his colleagues (*New York State Journal of Medicine*, June 15, 1959, **59**, 2359), 'no other drug has been as effective for specific treatment of migraine' as ergotamine tartrate. Although it can be given parenterally, the most practical route is either orally or rectally. Stress is laid upon the importance of administering the drug early in the course of the attack, and of adequate dosage. 'The optimal time of administration is in the prodromal period or, at least, not later than immediately after the onset of the headache'. The preparation they prefer is 'cafergot': two tablets followed by one tablet at half-hour intervals until the necessary effect is produced, or to a total of six tablets. Each tablet contains 1 mg. of ergotamine tartrate and 100 mg. of caffeine. Dosage, however, must be individualized: in some patients one tablet may be adequate for the initial dose, whereas others may require four. The average rectal dose of 'cafergot' is one suppository (2 mg. of ergotamine tartrate and 100 mg. of caffeine) every half-hour, a total of three suppositories being used if necessary. The maximum dose of ergotamine is 6 to 8 mg. in any one day, and this dose should not be given more than once a week. When ergotamine is given parenterally, not more than 0.5 mg. subcutaneously, or 0.25 mg. intravenously, should be administered in a single week. For those patients who respond poorly to ergotamine tartrate the best substitute is dihydroergotamine methanesulphonate: this can only be given parenterally, and the dose is 1 mg. intravenously, repeated in an hour if necessary. The contraindications to ergotamine are peripheral vascular disease, angina pectoris, impaired renal or hepatic function, and septic states associated with intravascular diseases, thyrotoxicosis, cachexia, avitaminosis, or pregnancy.

Chlorothiazide and Premenstrual Tension

'CHLOROTHIAZIDE is of value in relieving the subjective symptoms of premenstrual tension', according to L. B. Stevenson and C. Paul Hodgkinson (*American Journal of Obstetrics and Gynecology*, June 1959, **77**, 1286) as a result of their experience of its use in 50 cases. Their initial dosage was 250 mg. twice daily, but they found this inadequate and in the latter part of their investigation gave 500 mg. twice daily. 'It was found propitious to give the second dose no later than 2 p.m. if bothersome nocturnal diuresis was to be avoided'. Over 60% of their patients claimed to be 'substantially improved'. Improvement in mood was particularly marked, and painful breast engorgement was relieved in over 80% of the patients in whom this was a feature of the syndrome. Details are given of one patient, aged 36, with endometriosis of the pelvis, who lost 3 kg. in the five days before menstruation while taking 500 mg. of chlorothiazide twice daily. Although she reported relief from premenstrual œdema, headache and nervous tension, the pelvic pain and rectal pressure from endometriosis were not alleviated.

Hydrochlorothiazide in Hypertension

ATTENTION is drawn by J. A. Spittel, Jr., and his colleagues (*Proceedings of the Staff Meetings of the Mayo Clinic*, May 13, 1959, **34**, 256) to the fact that hydrochlorothiazide, the recently introduced oral diuretic, is 'a mild hypotensive agent when administered alone to patients with mild to moderate degrees of hypertension'. They give details of their findings in a series of 20 patients, aged 25 to 69, with essential hypertension, some of whom were in congestive heart failure, and all of whom were treated as outpatients. The dosage of hydrochlorothiazide

ranged from 25 to 200 mg. daily, amounts of more than 50 mg. a day being administered in divided doses. Hydrochlorothiazide produced a reduction of 12.9% in the average of the mean blood pressure of the 20 patients. In only one patient was there no fall in pressure at all. The usual effective dose was 75 to 100 mg. a day, and there was little added hypotensive action with doses exceeding 100 mg. a day. A significant increase in blood urea was observed in four of the 18 patients in whom serial determinations were made. In three of these it returned to pretreatment levels without discontinuation of therapy; in the fourth there was a partial fall. A significant decrease of serum potassium occurred in seven of the 18 patients in whom it was determined. In all but one it reverted to normal limits. In view of these findings, it is recommended that hydrochlorothiazide 'should be added with caution to the drug programme of a patient already receiving other antihypertensive agents'.

Treatment of Subungual Hæmatoma

PERFORATION of the overlying nail by a red-hot needle is the treatment of choice of a subungual hæmatoma, according to Jean Blavier (*Revue Médicale de Liège*, May 15, 1959, **14**, 337). The secret of success is to force the needle through the nail quickly and forcibly. If this is done, there is no pain, and there is very little risk of damaging the nail-bed because the intervening extravasation of blood prevents the point of the needle going as far as this. Once the nail is perforated in this way, the blood escapes and the patient gets immediate relief. The advantages of this method include the fact that no sterilization is required as the red-hot end of the needle is already sterile. In the second place, a needle or similar object, is always easily available. Thirdly, it can be carried out immediately. Actually the method is no use unless it is done within three to four days as by this time the blood is coagulated and therefore cannot escape through the hole made by the needle. Finally, no anæsthetic is necessary. After the blood has escaped, a loose dressing is applied, and the patient is advised not to put the finger in water until the nail has healed.

Pituitary Snuff and Nocturia

POSTERIOR pituitary snuff is of value in the treatment of nocturia in the elderly, according to R. W. Meikle, of the Royal Infirmary, Sheffield (*Journal of the American Geriatrics Society*, May 1959, **7**, 422). It was administered in the form of 'di-sipidin' by means of a specially designed insufflator to 11 patients, whose ages ranged from 70 to 91. The dosage was increased weekly from an initial level of one capsule (containing 100 mg., equivalent to 30 antidiuretic units) at 21.30 hours, and another one or two capsules at 23.30 hours, to a maximum of five capsules nightly. All the patients had been suffering from frequency, precipitancy, or occasional incontinence of urine for several weeks. Cases of neurological or neoplastic disease of the bladder and urinary tract, demented patients and those who were perpetually or doubly incontinent, were excluded from the trial. Cases of moderate prostatic hypertrophy, cystocele and uterine prolapse were accepted. Eight of the patients experienced some reduction in nightly frequency, and five of these were markedly improved. No obvious complications arose from its use, even after continuous administration for three months. Attention is drawn to the fact that it is easily administered by the patient, a nurse, or a relative.

Printers' Allergy

ALLERGIC reactions to gum arabic constitute an important occupational disease of printers, according to J. Turiaf and his colleagues (*La Semaine des Hôpitaux de Paris*, June 4, 1959, **35**, 1907) who have investigated their incidence in a Paris printing works. Of the 74 letterpress printers in the works, 69% had some form of allergic disorder, as had 53% of the offset printers. The most common reaction was allergic rhinitis which was present in 68% of the cases. Next in order of frequency came asthma (52%), followed by skin disorders which occurred in 31% of cases. The time of exposure before the onset of allergic manifestations was as short as a year in some cases, but on the average it was two to ten years. Rhinitis was the first manifestation, followed several months or years later by asthma. Skin tests showed that sensitization to gum arabic was usually associated with sensitization to other gums of vegetable origin and common allergens. The high incidence of rhinitis and asthma in this form of occupational allergy is due to the fact that the gum arabic is inhaled in a pulverized form. Analysis of the air in the typesetting room four hours after the start of work revealed a concentration of 45 mg. of gum arabic per cubic metre of air. There is no adequate means of treatment apart from change of occupation. The only sound treatment would be the abolition of the use of gum arabic.

REVIEWS OF BOOKS

Diseases of the Colon and Anorectum. Two Volumes. Edited by ROBERT TURELL, M.D. Philadelphia and London: W. B. Saunders Co., 1959. Pp. clxvii and 1238. Figures 634. Price £12 5s.

THESE two volumes of over 1200 pages compose the most important and comprehensive modern work on this extensive field of surgery. The authors form a wide cross-section of American surgery together with a smattering of British. The subject-matter attempts to cover all aspects of the etiology, pathology, diagnosis, treatment and complications of diseases of the rectum, colon and anus.

Half of the first volume is given to basic principles, and half to tumours of the large intestine. Embryology, anatomy and physiology are covered at length, but perhaps the chapter dealing with the abdominal wall, incisions and closure is somewhat superfluous in a book of this type. The same can perhaps be said of the chapters on electrolyte balance and anæsthesia. On the whole, the book is well balanced. Chapter 20, which concerns the method of spread of large-bowel cancer, the special dangers which occur at operation, and the methods which must be adopted to prevent dissemination, is particularly well presented. Every operation that is in use today for excision or restorative resection of rectal cancer is described. It is difficult to distinguish the advantages of some, although all, apart from the synchronous combined excision (two-team), which is the most frequently used operation at St. Mark's Hospital in London, are well described.

The second volume covers a wide diversity of subjects, and contains much information. The degree of importance attached to some diseases would seem strange to many, and the chapter on rectal prolapse is disappointing. The book, however, remains the best new book of recent years in its field. It is readable, has limited references but good indexing.

Synopsis of Skin Diseases. By BETHEL E. R. SOLOMONS, JR., M.D., F.R.C.P.I. Bristol: John Wright & Sons Ltd., 1959. Pp. 304. Figures 14. Price 30s.

THE aims stated by the author in the preface are that: 'The book is intended for the busy practitioner, for those who have to revise the subject rapidly and also for the student about to take his final examination. It does not replace the larger scope of a textbook.' In reviewing the book, these objects have been kept in mind, and the book has been consulted for every condition which has turned up during the day in hospital and private practice; not once has it been found wanting. The descriptions given are expressive, short and to the point, and discussion, where necessary, is well presented, and treatment follows generally accepted lines. The balance of the book is right, the common dermatoses having most of the space, but the uncommon are also mentioned adequately. The appendixes contain a useful list of concentrations of potential irritants for patch testing and formulæ of commonly used preparations.

To sum up, this is a most useful book and the author has achieved his aims admirably. As a quick accurate reference book it is recommended unreservedly.

Modern Trends in Diseases of the Vertebral Column. Edited by REGINALD NASSIM, B.M., F.R.C.P., and H. JACKSON BURROWS, M.D., F.R.C.S., F.R.A.C.S. London: Butterworth & Co. (Publishers) Ltd., 1959. Pp. ix and 303. Figures 172. Price 75s.

THIS is a collection of essays on different aspects of spinal disorders, each of which is written by an authority. It is not a comprehensive book: e.g. details of operative surgery are not included and several important spinal conditions are considered only briefly. Lumbar disc protrusions warrant a chapter to themselves. Tuberculosis is a diminishing problem in this country, but not in many parts of the world where this book will be read; therefore the account given might well have been expanded.

Any book of multiple authorship is liable to repetition. This fault is largely avoided, but spondylolisthesis is discussed under congenital anomalies and again under low back pain, whilst osteoporosis is a recurring topic in chapters other than the one devoted to this subject. The discussion of anatomy and development is a masterly exposition of the basic facts, the chapter on radiology includes a clear description of technique in relation to bone density, and the account of vertebral tumours is amplified by well-chosen references. The various chapters upon clinical topics include a concise account of structural scoliosis and a discussion of low-back pain which will be of the greatest value to any general practitioner. The orthopædic surgeon reading this book will be struck by the ways in which physicians and neurologists differ from him in their viewpoints upon the common conditions which present at his clinics. If the wide definition of cervical spondylosis is accepted, few would agree with the neurologists' statement that the neck symptoms are rarely obtrusive; they may indeed be a source of great pain and

prolonged disability, but the objective signs being slight are possibly less likely to be referred to a neurologist. The symptoms being thus minimized, the great value of manipulative treatment is not discussed.

The book is beautifully produced, but of correspondingly high price. The only serious misprint is that the dominant extensor muscle of the knee-joint is called the *quadratus femoris* (p. 264).

Heredity Counseling. Edited by HELEN G. HAMMONS. New York: Paul B. Hoeber Inc.; London: Cassell & Co. Ltd., 1959. Pp. xv and 112. Price 28*s*.

THIS book places on record the papers read at a recent symposium sponsored by the American Eugenics Society. It is not a comprehensive textbook on the subject of the information and advice that can be given to patients concerned about inheritable disorders. The first part of the book, on genetics in medical practice, consists of four contributions, two of which are of great genetical interest and value: one by Witkop on inherited disorders in dentistry and the other by Witkop and collaborators on the methods used and some results found in a field survey of a population isolated in Maryland. The second part consists of ten contributions on heredity counselling. The authors mostly give a personal account of the type of problem encountered in genetics clinics and the principles which they have evolved for the organization and conduct of such clinics. Their experience will be of interest and value, especially to those doctors responsible for the growing number of genetics clinics in this country.

Cardiovascular Sound in Health and Disease. BY VICTOR A. MCKUSICK, M.D. Baltimore: The Williams & Wilkins Co.; London: Baillière, Tindall and Cox, 1959. Pp. xii and 570. Illustrated. Price £5 10*s*.

PHONOCARDIOGRAPHY has played an important part in forming an international language of auscultatory physical signs and has thus helped to advance the diagnostic precision attainable by clinical examination. In this excellent book Dr. McKusick gives a balanced account of the position reached today in our knowledge and interpretation of cardiovascular sound. The history of auscultation and later of the development of phonocardiography is outlined. Every aspect of cardiovascular sound is dealt with: the physics of sound production, points of detailed anatomy and physiology that determine sound formation, recording methods, and finally the clinical significance and interpretation of sounds. What is particularly striking about the book is the catholic outlook of the author, who mentions every theory advanced to explain a particular problem, putting the arguments simply for and against each view, and leaving the reader to form his own opinion from the evidence presented. Although, perhaps, not everyone will share Dr. McKusick's preference for spectral phonocardiography as opposed to conventional phonocardiography, there is no doubt that this more complicated and tedious method of recording gives the most detailed and complete record of cardiovascular sound that is possible today.

The book, which is well illustrated, presents a readable and comprehensive synopsis of present-day knowledge of cardiovascular sound and incorporates an excellent bibliography.

Mental Illness in London: Maudsley Monographs No. 6. BY VERA NORRIS, M.B., PH.D. London: Chapman and Hall Ltd., 1959. Pp. 317. Figures 11. Price 35*s*.

IT is to be hoped that, when the new Mental Health Act becomes law, there will be a general development on the line of the more successful of the experiments already made by enterprising Regional Hospital Boards and local authorities. In planning so far it has often had to be taken for granted that the demand for any service offered will always be so much in excess of the facilities provided that the matching of supply and demand needs no detailed study. This has been inevitable because of the very scanty information available about the incidence, distribution and outcome of the principal psychiatric disorders, major and minor. In those areas where detailed studies have been made, the results have suggested that the amount of psychiatric disability of one kind or another is so great as to be almost beyond the financial resources of the community unless its mental health is given an entirely different priority in the minds of those who control the public purse. The lack of clear statistical fact has also allowed claims to be made which cannot be refuted—notably on the results of physical treatments of psychotherapy and of community care. With the present prospect of rapid expansion in the Mental Health Services, this book is most timely for it not only provides most valuable information but sets an example and a standard of how statistics may be applied and made meaningful in terms of future needs.

The investigation described is based on the patients admitted over a three-year period to two of the mental observation units established by the London County Council before the advent of the National Health Service and of three mental hospitals. It deals with their diagnosis, mortality, prognosis, disposal and the extent to which they required the help of the

Mental Health Services. It has involved a detailed study of 10,000 clinical records and an expenditure of skilled effort equivalent to the work of eight investigator/years. The results allow of a thorough study of such subjects as consistency of diagnosis, prognosis of manic-depressive states and schizophrenia and the mortality of mental hospital patients. Important conclusions are reached as to the expectation of the different types of illness in the general population. In each section the results are compared with those of studies in other areas where methods of comparable rigour have been adopted and the material set out will stand the scrutiny of both statistics and common sense.

This sixth Maudsley Monograph is a credit to the series and will clearly be quoted and referred to for many years to come. It is deeply to be regretted that Dr. Norris did not live to see it published and to hand on to others personally the methods she had so carefully evolved.

The Mast Cells. By JAMES F. RILEY, M.D., PH.D., D.M.R.T., F.R.C.S.ED. Edinburgh: E. & S. Livingstone Ltd., 1959. Pp. x and 182. Figures 65. Price 30*s.*

MAST cells were first described as a differentiated type of cell by Ehrlich in 1879. Their exact function is not yet completely analysed but this monograph discusses the earlier views and the recent findings, histological and physiological, so that a more balanced picture is now possible in a number of species. Ehrlich's view that they are functioning cells of connective tissue is confirmed. Their development follows fibroplasia, normal or pathological. Enormous numbers are found in the serosæ as well as around small blood vessels. In the latter case as they mature they seem to move away from the vessels. Their relationship to histamine and heparin is discussed in great detail. Certain tumours rich in mast cells show exceptionally high histamine values but in these cases the heparin content may not show correspondingly high values. From a study of the histamine liberators it is concluded that the preformed histamine in the mast cell is only held loosely as part of a loose complex containing heparin and basic proteins. In rats the granules also contain phosphatidyl ethanolamine and it may be by an effect on this latter substance that the histamine is set free. Antihistamine drugs are known to protect the granules of the mast cells under certain conditions. The classical histamine liberators all produce pathological effects on the granules but under normal conditions histamine may be liberated without such changes. Further, not all the cell histamine is necessarily liberated by these substances and certain tissues may show a high histamine content without showing a large number of mast cells: e.g. the mucosa of the rat pylorus.

Anyone interested in the mast cell will find this book essential. It has the advantage of being written by one of the most active members of the Dundee group who have done so much work in this field and is a book to be read and used.

Family Influences and Psychosomatic Illness. By E. M. GOLDBERG. London: Tavistock Publications Ltd., 1959. Pp. xii and 308. Price 38*s.*

THE subtitle of this book is 'An inquiry into the social and psychological background of duodenal ulcer'. The conclusions of the inquiry occupy nine pages and would lend themselves badly to compression into a few sentences for this review. They are about the mothers and the fathers of sons with duodenal ulcer, about the sons themselves and their childhood. A just detectable pattern emerges when the 32 young men with ulcers are compared with 32 controls. The study differs from any previous study because it attends to the parents as well as to the sufferers. Even where it overlaps other studies, its conclusions do not entirely confirm their conclusions. Thus we are left with the impression that we are peeping at work in progress—work which may one day lead to important conclusions but has not done so yet.

The book is fair and painstaking. The authors are careful not to assume that psychological or social factors are the only possible causes of duodenal ulcer. Their conclusions are the less striking because care has been taken not to force the evidence. The book is written at a depth to which general practitioners cannot afford to plunge in more than one or two subjects which may be their special interest. Nevertheless it points to new facets of their ulcer patients to which they might valuably pay attention. It also casts light on present-day trends in family relationships generally, and thus again comes into the general practitioner's field.

Obstetric and Gynecologic Milestones. By HAROLD SPEERT, M.D. New York and London: The Macmillan Co., 1959. Pp. ix and 700. Figures 79. Price £5 5*s.*

THIS is a book which ought to be in the hands of everyone who is interested in the history of obstetrics and gynæcology. It is beautifully produced and superbly illustrated. It has 79 chapters, each constituting a separate essay, independent of the others. The essay deals primarily with one subject, together with the author or authors who have achieved immortality through it. Each chapter contains a short

biography of the men whose names head its chapters and at the end of each there is a list of references. Dr. Speert writes in the preface that a high degree of selection has been necessary to keep this work within the bounds of one volume and this must be accepted. There are also many milestones in obstetrics and gynæcology that have not had the names of the men who set them up carved upon them and it is clear that a name has sometimes stuck luckily rather than justly. Of the hundred or so famous doctors named in the chapter headings, no less than three—Pfannenstiel, Porro and Schuchardt—died of infection contracted at operation.

One can spend many fascinating hours reading this attractive book with its praise of famous men.

NEW EDITIONS

The Treatment of Diabetes Mellitus, by Elliott P. Joslin, Howard F. Root, Priscilla White, and Alexander Marble, in its tenth edition (Henry Kimpton, £6 2*s*. 6*d*.) retains its pre-eminent position as the universally recognized standard textbook on the subject. The senior author, now a nonagenarian who has lost none of the crusading fervour with which he has led the campaign to control diabetes in his own country, has amassed in his time a wealth of information on the subject unequalled elsewhere in the world. His book is therefore no theoretical dissertation, but the distillation of his experience with over 50,000 patients. The first to use insulin in the United States, he has always been to the fore in trying out new forms of treatment, and in this new edition of his book his assessment of the new oral hypoglycæmic agents is based upon a personal experience of at least 3000 patients. For an authoritative review of diabetes in all its aspects this book still stands supreme.

An Introduction to Medical Genetics, by J. A. Fraser Roberts, M.D., F.R.C.P., in its second edition (Oxford University Press, 35*s*.) provides an admirable review of the subject for the novitiate. It is not easy reading but, at least so far as the reviewer is aware, there is no other book which presents the principles of medical genetics more clearly. To the medical student of thirty years ago genetics was a subject forgotten long before his clinical period. Today it is a subject of which no practitioner can afford to be ignorant. This is the book which will supply him with the essentials of this rapidly expanding branch of medicine.

Parsons' Diseases of The Eye, by Sir Stewart Duke-Elder, G.C.V.O., M.D., F.R.C.S., in its thirteenth edition (J. & A. Churchill Ltd., 50*s*.) has undergone careful revision. All the many advances in ophthalmology since the last edition was published five years ago have been incorporated and critically assessed. For half a century this has been the standard textbook on the subject for students and general practitioners. This new edition ensures that it will continue to occupy this proud position. There is no other book which contains such a sound, practical, comprehensive review of the subject in such a relatively small space. This is definitely one of the essential books for the general practitioner.

Pain, by Harold G. Wolff, M.D., and Stewart Wolf, M.D., in its second edition (Blackwell Scientific Publications, 32*s*. 6*d*.), in the words of the authors, 'offers a brief synthesis of the current thinking on pain in the perspective of some of the important past developments'. As such it is an excellent book for the practitioner. As a practical guide to therapy it is not so valuable, but in view of the pre-eminence of pain as a presenting symptom in general practice the book deserves careful study by all practising clinicians.

Applied Anatomy for Nurses, by E. J. Bocock, S.R.N., S.C.M., D.N., and R. Wheeler Haines, M.B., D.SC., F.L.S., in its second edition (E. & S. Livingstone Ltd., 17*s*. 6*d*.) does not depart very much from the previous edition. The problem of compressing a large amount of information into a small text has been boldly faced by the authors with very satisfactory results, but of necessity in so doing, absolute accuracy has had to be sacrificed to brevity and clarity. It is perhaps a pity that the preface tells us that we shall get a smile from figure 115 when it is, in fact, figure 118 that is intended, and it is also difficult to see the justification for the introduction of A.I.G. and P.I.G. for anterior and posterior interventricular groove when these terms are not introduced again in the text. The line and stipple drawings are clear and helpful, and this text will continue to provide an interesting and readable introduction to anatomy for nurses.

The contents of the September issue, which will contain a symposium on 'Immunization in General Practice,' will be found on page A 102 at the end of the advertisement section.

Notes and Preparations see page 241.
Notes from the Continent see page 245.
Fifty Years Ago see page 247.
Motoring Notes see page A 87.
Travel Notes see page A 91.
Bridge Notes see page A 95.

NOTES AND PREPARATIONS

NEW PREPARATIONS

'AMOXAL' preparations are intended for the treatment of fungal infections. They are available as a gel, which 'with its alcoholic base is highly effective for the majority of tinea infections especially athlete's foot', as a cream for use in dry, scaly or raw lesions, and as a dusting powder for use concurrently and to prevent reinfection. The gel and the cream contain 2% amyloxybenzamide, 2% amyloxyacetophenone, and 1% salicylic acid, and are available in tubes of 25 g. The dusting powder contains 2% amyloxybenzamide and 0.5% hexachlorophane, and is available in a polythene puffer pack of 40 g. (Smith & Nephew Pharmaceuticals Ltd., Bessemer Road, Welwyn Garden City, Herts.)

'TYRIMIDE' tablets each contain 5 mg. of isopropamide iodide, and are intended for 'the anticholinergic management of a wide range of gastro-intestinal disturbances'. The usual dosage is one tablet every 12 hours, which is said to provide uninterrupted effect and 'remarkable freedom from troublesome side-effects'. They are contraindicated in patients with glaucoma, pyloric obstruction or prostatic hypertrophy. Available in containers of 30 and 250. (Smith Kline & French Laboratories Ltd., Coldharbour Lane, London, S.E.5.)

PHARMACEUTICAL NOTES

BURROUGHS WELLCOME & CO. LTD. announce that 'darenthin' (bretylium tosylate), which is said to be of 'great potential importance' in the treatment of hypertension, is being issued in limited quantities to units undertaking clinical trials. Supplies are not yet available for general use. (The Wellcome Building, Euston Road, London, N.W.1.)

FBA PHARMACEUTICALS LTD. announce that 'resochin' tablets, containing 0.25 g. of chloroquine phosphate, are now being presented as special lacquered tablets. These are tasteless and 'the possibility of gastric upset, sometimes associated with long-term chloroquine therapy, will be considerably lessened'. (37-41 Bedford Row, London, W.C.1.)

ROUSSEL LABORATORIES LTD. announce that 'dexacortisyl' tablets are now available in an additional strength (0.75 mg.) in packs of 20, 100 and 500. (847 Harrow Road, London, N.W.10.)

WARD, BLENKINSOP & CO. LTD. announce that their skin antiseptic 'penotrane tincture' is now available as a colourless preparation which will in future be supplied against all orders unless 'penotrane tincture (red)' is specified. (York House, 37 Queen Square, London, W.C.1.)

NEW APPARATUS

'CALNAMESH' is the name of a new, non-woollen hospital blanket 'specially designed to eliminate dust, so reducing ward work and helping to control serious cross-infection'. It consists of a cellular, mesh-fabric material of viscose staple cotton, quilted between two cotton and viscose sheets to provide maximum insulation against loss of heat, and fitted with side flaps of single sheeting for 'tucking in'. (Slumberland Ltd., Redfern Road, Tyseley, Birmingham.)

FILM NEWS

A Simple Method of Cataract Extraction using Zonulysin (Alpha-Chymotrypsin) (16 mm., colour sound; running time 16½ minutes) has been produced for S. Maw Son & Sons Ltd. Full details may be obtained from the Pharmaceutical Marketing Manager, S. Maw Son & Sons Ltd., Aldersgate House, Barnet, Herts.

Enquiry into General Practice (16 mm., sound; running time 30 minutes) examines the place of general practice in modern society and is intended to provoke discussion. Produced for the *Medical World*, it is available on free loan for showing to medical audiences, medical students and social workers and is distributed through the B.M.A. Film Library, or Sound Services Ltd.

Poise and Movement (16 mm., sound; running time 21 minutes) is the third in the series of nurse-training films made for the Ministry of Health, to demonstrate how good posture and correct movements can ease the task of nursing. Available from the Central Film Library, Government Building, Bromyard Avenue, London, W.3, price £17 or on loan at a cost of 10s. for the first day and 2s. for each subsequent day.

The *First International Congress of Endocrinology* will be held at the Technical University of Denmark, Copenhagen, from July 18 to 23, 1960. Full details may be obtained from the Congress Secretariat, First International Congress of Endocrinology, Hormone Department, Statens Seruminstitut, Copenhagen S, Denmark.

COURSES AND CONFERENCES

Two *postgraduate courses in occupational health* have been arranged for the Autumn, one at the

London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1, from September 28 to October 3, and the other at the Nuffield Department of Occupational Health, University of Manchester, from November 2 to 7.

Depression will be the subject of a symposium organized by the Postgraduate Medical School of the University of Cambridge, to be held in Cambridge from September 22 to 26, 1959, inclusive. Full details may be obtained from the Secretary, Medical School, Tennis Court Road, Cambridge.

The Health of Business Executives will be the subject of a one-day conference for directors and executives in commerce and industry to be held at the Royal Festival Hall on November 20, 1959. Full details may be obtained from the Director-General, The Chest and Heart Association, Tavistock House North, Tavistock Square, London, W.C.1.

B.M.A. PRIZES

THE Council of the British Medical Association announces the following prizes:—*Sir Charles Hastings and Charles Oliver Hawthorne Clinical Prizes* (£75 and £50) for the best entries based on systematic observation, research and record in general practice.

Provisionally Registered Practitioners' Prize (£50) for the best essay on 'What defects do you now recognize in your medical education, and how do you think they might be remedied in future?'.

Medical Students' Prizes (£25 each) for the best essays on 'Why I chose Medicine and what I hope to achieve'.

Closing date for entries for all these awards is December 31, 1959, and full details may be obtained from the Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

THE MEDICAL DIRECTORY 1960

THE Editor of *The Medical Directory* writes: 'The annual schedule, upon the return of which the accuracy of *The Medical Directory* mainly depends, has recently been posted to all traceable members of the medical profession, and its speedy return would be appreciated. Any doctor who has not received the annual schedule, or who has mislaid it and would like a duplicate, is requested to communicate as soon as possible with The Editor, *The Medical Directory*, 104 Gloucester Place, London, W.1. The full name and year of qualification of the doctor should be sent for identification'.

PANMINERVA MEDICA

ON the occasion of the jubilee of *Minerva Medica*, the Minerva Medica Editorial Group, under the energetic leadership of Professor T. Oliaro, has launched upon the ambitious project of publishing in English a monthly review of Italian medicine, entitled *Panminerva Medica*. The first issue, which is dated May 1959, is an admirably produced journal. As the Minerva Medica Editorial Group is responsible for the publication of over forty journals, it can provide ample coverage for a journal such as this. The annual subscription is £3 10s. (or $10), and subscriptions should be addressed to: Panminerva Medica, Corso Bramante 83-85, Turin, Italy.

EARLY PHARMACIES

THE WELLCOME FOUNDATION has now been able to re-erect five of the reconstructions of early pharmacies which formed part of the Wellcome Historical Medical Museum before the last war. These consist of a sixteenth-century Italian pharmacy, an eighteenth-century Andalusian pharmacy, a centuries-old Arab pharmacy, a seventeenth-century English pharmacy and the original front of John Bell's pharmacy founded in Oxford Street in 1798. These are now on show at the Wellcome Building, Euston Road, London, N.W.1.

DOMICILIARY CONSULTATIONS

THE quinquennial report of the Sheffield Regional Hospital Board, for 1952 to 1957, shows a marked increase in the number of domiciliary consultations: from 15,858 to 22,308. This last figure is nearly double that for 1949. The most marked increases have been in psychiatry (255 to 1,648), chest diseases (198 to 1,121) and orthopædics (700 to 1,525). A random sample of 2,711 consultations showed that 27% of those seen were sent to hospital, 14% were placed on a waiting list, and home treatment was prescribed for 55%. In this sample, the general practitioner is recorded as being present at the consultation in only 56% of cases. In 27% he was not present and details are not available of the remaining 17%.

BCG VACCINATION

SINCE 1951, WHO and UNICEF have assisted the governments of 41 countries and territories, with a combined population of 785 million, in carrying out BCG vaccination campaigns against tuberculosis. In the course of these campaigns, approximately 234 million persons have been tuberculin tested, and 88 million vaccinated. A preliminary review of the findings shows that the degree of protection given is in the region of 80%, and it is concluded that BCG vaccina-

tion 'should have an important place in, and form an integral part of, the tuberculosis programme in most countries'.

ROYAL JELLY AND LEUKÆMIA

In view of the current popular interest in royal jelly it is of interest to note that in a recent issue of *Nature* (1959, **183**, 1270) G. F. Townsend and his colleagues report that 'admixture of royal jelly with tissue cells before inoculation completely suppresses the development of a transplantable mouse leukæmia and the formation of ascitic tumours in mice. Fractionation studies have established that this anti-tumour activity resides in the main fatty acid of the royal jelly—10-hydroxydecenoic acid'. This effect was obtained only when the active material was mixed with the cells before administration. Attempts to demonstrate protection after tumour infliction have so far been unsuccessful. These results, it is claimed, have been confirmed repeatedly in nearly a thousand mice during a two-year period, 'and show a striking effect: either all the mice die or all survive'.

MULTIPLE BIRTHS

It is announced from Mozambique that a 29-year-old mother who had quintuplets twenty months ago has given birth to her second set of triplets. Since her marriage she has had two sets of quintuplets—all of whom died soon after birth. Of the 19 children she has had, only the new triplets and an 11-year-old daughter survive.

HIBERNATION IN DYSENTERY

The use of artificial hibernation has reduced the death rate from toxic dysentery, in Peking, from 22.8% to 4.2%, according to Chu Shou-Ho (*Chin. med. J.*, 1959, **78**, 120). The rationale of this form of treatment is that 'the onset of toxic dysentery and the subsequent changes leading to the rapid death of patients point to a sudden attack on the central nervous system. . . . Hence . . . protection of the central nervous system from serious damage . . . is of primary importance. There will then be time for the antibiotics to act on the infection. . . . Artificial hibernation puts the central nervous system under a state of protective inhibition against sudden exogenous stimuli, reduces the body metabolism, diminishes oxygen consumption, and enables the patient to recover from the state of shock'. Details are given of the method used in 95 cases of toxic dysentery in children, in whom the body temperature was retained at around 36°C. for twelve to twenty-four hours. All but four of the children recovered.

LIP-BITING AND ANÆMIA

Lip-biting may be a symptom of anæmia, according to Ikuzo Minato (*Tohoku J. exp. Med.*, 1958, **69**, 39). He first noticed it in two school children: a girl aged 12 and a boy aged 10. He gives the blood counts of five children whom he selected during a school medical examination because of their lip-biting, and their hæmoglobin ranged from 55 to 72%. It is pointed out that 'the lip-biting consisted not in lip-licking, but in biting the lower lip with upper teeth, much less often in biting the upper lip with lower teeth'. It is suggested that lip-biting may be a useful sign of anæmia in patients who are not obviously anæmic on clinical examination.

PUBLICATIONS

Adoption, by Margaret Kornitzer, is a first-class little book. Written primarily, and simply, for intending adopters and for those who have already undertaken adoption it should be studied by medical practitioners and social workers who so often find themselves involved in the various problems and difficulties involved. The legal side is fully dealt with, including the modifications in the law which came into force on April 1, 1959. The human side, however, is the author's strong point. She knows what sort of questions adopters should and do ask themselves, and her answers are convincing in a practical yet kindly way. When, how and how much to tell the child (and relations or neighbours) are extremely well set out. (Putnam & Co. Ltd., price 10*s.* 6*d.*)

The Nurse and the Diabetic, by Joan B. Walker, M.D.—This addition to the *Nursing Mirror* books is both welcome and necessary. The nature of diabetes and the common clinical types are adequately described, and the important subject of syringes, insulin strengths and dosage is well and clearly presented but, under the heading of 'Method of injection' (page 29, line 1) the word intradermally should be substituted for subcutaneously. The role of the health visitor and home management of the diabetic are subjects on which the author is specially qualified to express an opinion. The illustrations add to the usefulness of the text but, in those of the technique of insulin injections, the sites, from the point of view of fat atrophy, are unsuitable. On the whole a successful attempt to cover a large field in a brief, simple and concise manner. (Iliffe & Sons Ltd., price 10*s.* 6*d.*)

R.A.F. Handbook of Preventive Medicine, edited by Wing Commander W. B. Thorburn, M.B., CH.B., D.P.H., D.I.H., second edition.—The widening scope of Air Force medicine is indicated by the inclusion in this edition of

chapters on mental health, occupational health, toxic substances, medical statistics and the risks in handling radioactive substances. (H.M. Stationery Office, price 40*s*.)

Some Facts About Cerebral Palsy is a pamphlet in question and answer form intended for those requiring 'some introductory background information' on cerebral palsy. (British Council for the Welfare of Spastics, 13 Suffolk Street, Haymarket, London, S.W.1, price 1*s*. 6*d*.)

The Occupational Therapist is the second edition of a booklet in the 'Choice of Careers' series issued by the Youth Employment Executive of the Ministry of Labour and National Service. It describes the day-to-day work of occupational therapists, gives details of the qualities and training required, and ends with a chapter on 'Openings and Salaries'. (H.M. Stationery Office, price 6*d*.)

Chest and Heart Disease in the Commonwealth 1958 is the full transactions of the N.A.P.T. Commonwealth Chest Conference which was held in London in July 1958. (The Chest and Heart Association, price 35*s*.)

Young Endeavour, by W. C. Gibson, D.Phil., M.D., C.M., is an account of the contributions made by some of the leading men in medicine while they were yet students. It ranges widely and includes names such as Vesalius, Astley Cooper, Pavlov, Virchow, and Martin Flack. As the author points out, it is doubtful whether the current packed medical curriculum is as conducive to original thinking as the more leisurely curriculum of the past. (Blackwell Scientific Publications, price 50*s*.)

OFFICIAL PUBLICATIONS

Report of the Medical Research Council for the Year 1957-58 records a further expansion of the Council's activities, including arrangements for the establishment of seven new research units and groups. In 1938 there were only five such establishments; at the end of the period covered by this report there were 68. Within the last three years alone the Council has set up 21 new research units and groups. In the financial year ended March 31, 1958, the total expenditure of public funds by the Council was £3,032,889 on ordinary account and £35,514 on non-recurrent account.

As in recent years, the report contains a useful section dealing with trends in medical research. Among the subjects discussed are 'Research in general practice', 'The viruses of trachoma and inclusion blennorrhœa', 'Mammalian fertilization', and 'Rehabilitation of Chronic Schizophrenics'. (H.M. Stationery Office, price 13*s*.)

Report of the Ministry of Health for the year ended 31st December, 1958. *Part I.*—This deals predominantly with the administrative aspects of the National Health Service. In his introduction the Minister of Health comments: 'For the future the battle for health must be fought more and more in the community, with the family doctor as the leader of the clinical team and the local authority supporting him with the help of the public health medical, nursing and welfare staff'. In this connexion it is of interest to note that in the financial year 1957-58 the net expenditure of hospital authorities was £338.7 million (including £12.5 million on drugs and dressings), whilst the expenditure in the general medical services was £62.8 million. In addition, the net expenditure on the pharmaceutical services was £53.3 million. The number of merit awards to consultants in England and Wales at December 31, 1958, was: 'A' awards (£2,500 per annum) 279; 'B' awards (£1,500 per annum) 698; 'C' awards (£500 per annum) 1,397. (H M. Stationery Office, price 15*s*. 6*d*.)

The Medical Service of the Royal Navy

VACANCIES FOR MEDICAL OFFICERS

Candidates are invited for Short Service Commissions of 3 years, on termination of which a gratuity of £600 (tax free) is payable. Ample opportunity is granted for transfer to Permanent Commissions on completion of one year's total service. Officers so transferred are paid instead a grant of £1,500 (taxable).

All entrants are required to be British subjects whose parents are British subjects, medically qualified, physically fit, and to pass an interview.

Full particulars from the Admiralty Medical Department, Queen Anne's Mansions, St. James's Park, London, S.W.1.

NOTES FROM THE CONTINENT

A European Newsletter

ITALY

Meprobamate in midwifery.—G. Giorgetti and T. Maggiora-Vergano have investigated the efficacy of meprobamate as an obstetric analgesic in a series of 100 cases of labour characterized by cervical dystocia, inadequate dilatation of the cervix, severe pain and marked psychological excitement. The drug was given orally: an initial dose of 400 mg., followed by 200 mg. four hours later. As judged on a subjective basis, the tranquillizing effect was good in 18 cases, fairly good in 19, slight in 41, and absent in 22, whilst the analgesic effect was good in 12 cases, moderate in 39, and absent in 49. As judged objectively by observation of the patient during labour, the results were rather more satisfactory, the tranquillizing effect being good in 53 cases, fairly good in 10, slight in 17, and absent in 20. Assessed according to the effect on spasm of the cervix, the results were good in 22 cases, moderate in 21, and absent in 47. No toxic effect was observed upon either the mother or the child.

In view of these findings the authors recommend that meprobamate should not be used routinely in labour. They also consider that its use is contraindicated in what has come to be known as the psycho-prophylactic method of childbirth. On the other hand, in abnormal cases such as those they have studied in this investigation, and in women inadequately prepared psychologically for childbirth, they consider that the results are sufficiently encouraging to justify further investigation.

Rupture of the spleen in children.—Three cases of traumatic rupture of the spleen in children are reported by C. Giordani. The first was a child aged 9 years, in whom the rupture occurred in two stages. The first stage consisted of a subcapsular rupture as a result of falling downstairs and hitting his left side against the edge of a step. This was followed by rupture of the capsule during a fit of laughing. The second was a child aged 11 years who was thrown against a paling while sledging. The third, also a child aged 11, had such severe pain from intestinal obstruction caused by *Ascaris lumbricoides* that he threw himself from a car and fell on his left side. All three had marked rigidity of the abdominal wall, with referred pain in the acromial region (Kehr's sign). In the third child this was so severe that he was suspected of having a dislocated shoulder. In the author's opinion this sign is pathognomonic of a ruptured spleen. Neither Saegesser's sign (pain on pressure between the clavicular insertion of the sternocleido-mastoid muscle and the scalenus medius) nor Delannoy's sign (peri-umbilical ecchymosis) was present in any of the three cases. Ballance's sign (shifting dullness in the right flank but not in the left flank) was present in the second case. Diagnosis was relatively easy in the first two cases. In the third it was difficult because of the symptoms and signs resulting from the intestinal obstruction.

Treatment consisted of splenectomy in the first two cases. In the third case attempted freeing of the spleen, firmly fixed by adhesions, resulted in a fatal cardio-circulatory reflex.

Local hydrocortisone in post-traumatic bursitis.—N. Gennai has treated 13 cases of post-traumatic bursitis by means of local injections of hydrocortisone acetate. The dosage was 25 to 40 mg., with a maximum total dose of 50 to 100 mg. The interval between injections was three to eight days, with an average of four to five days. A rapid and permanent cure was obtained in nine cases. Two patients required admission to hospital, and in another two there was a relapse but this responded to a second course of injections. The best results were obtained in cases of recent onset, the response being slower in more chronic cases. From the practical point of view the great advantages of this form of therapy are the shortening of the period of incapacity for work, the reduction in the incidence of chronic sequelæ, and therefore in the incidence of permanent invalidism. All the patients were treated as outpatients.

Heart failure in infancy.—Details of 25 cases of acute primary heart failure during the first year of life are given by S. Cavalieri and P. Montenovesi. They consisted of 10 cases of myocarditis, four cases of fibro-elastic myocarditis, three cases of endocardial fibro-elastosis, five cases of undetermined etiology, two cases of acute arrhythmia, and one case of myocardiosclerosis. The prodromal symptoms include restlessness, dyspnœa and respiratory crises. Once the condition is established, the manifestations include tachycardia, paroxysms of coughing and cyanosis, and psychomotor agitation. Examination reveals the presence of cardiac enlargement, though this may not be marked, atypical cardiac murmurs, electrocardiographic changes, and enlargement of the liver. The prognosis is poor. It is noted that endocardial fibro-elastosis is often accompanied by inflammation of the myocardium.

=81%*

"The highest percentage of symptomatic relief is obtained by early and adequate administration of ergotamine tartrate and caffeine alone or combined with antispasmodics and/or sedatives."
(J.A.M.A., 1957, 163, 1111.)

ORGRAINE

DEFEATS

MIGRAINE

* 2034 of 2511 patients in the above series were successfully treated by the combination of drugs on which ORGRAINE is based.

ORGRAINE fast disintegrating tablets give quickest possible relief with oral treatment and enable smaller doses of ergotamine tartrate to control the vasodilatory (headache) phase of migraine.

Composition (per tablet)		Action
Ergotamine Tartrate B.P.	1.0mg.	→ constricts dilated cerebral arteries.
Caffeine B.P.	100.0mg.	→ potentiates ergotamine.
Hyoscyamine Sulphate B.P.C. (1949)	0.0875mg.	→ alleviates nausea and vomiting.
Atrophine Sulphate B.P.	0.0125mg.	
Phenacetin B.P.	130.0mg.	→ relieves residual occipital pain.

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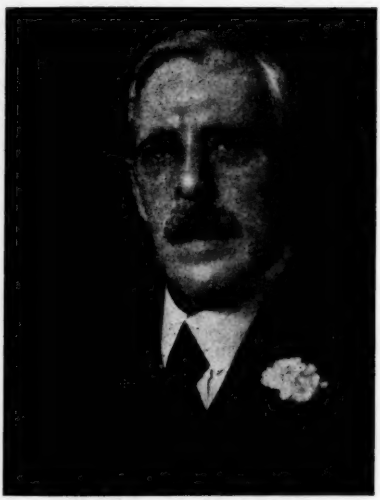
THE PRACTITIONER
Fifty Years Ago

'We are living in a phase of evolution which is known as the twentieth century and stands for a certain achieved growth of the human mind. But the enormous majority of the human race do not belong to that phase at all . . . . Victorians, Tudorians, ghosts surviving from the Middle Ages, and multitudes whose minds properly belong to palæolithic times, far outnumber the people who truly appertain to the twentieth century'.—Robert Briffault, *Rational Evolution.*

AUGUST 1909

'THERE was a time not so far distant', 'Notes by the Way' remind us, 'when specialism was looked upon as being in itself a stamp of quackery. Conservatism is always strong in the medical synagogue; this is natural seeing that the high priests of the profession have necessarily reached the age when the human mind, according to Goethe, becomes impervious to new ideas. At an opening address delivered to the Medical Society of University College, London, the late Sir John Russell Reynolds, in 1881, denounced specialism as retrogression rather than evolution, and as the survival not of the fittest, but of the charlatan and the quack. . . . Sir John . . . said that he had known "distinguished surgeons go down into the country to say whether or no a patient with rheumatic fever had endo- or pericarditis, when neither of them would know which end of the stethoscope to use". . . . We have known a galaxy of consultants who agreed that the proper course was to feed up a young man sore stricken with syphilis, nonplussed when the patient told them that owing to the ulcerated state of his throat, which they had not attempted to examine, he was unable to swallow. A specialist had to be called in to treat the case, whereupon the consultants retired in disgust'. The Editor also tells a delightful story of Sir Henry Butlin: 'When it became evident to the medical staff at St. Bartholomew's Hospital that if proper instruction was to be given to their students a department for diseases of the throat must be created, Mr. Butlin, being the junior assistant surgeon, was, as he said, pitchforked into the charge of a specialty which he did not care about, and expected to treat patients whose diseases he could not diagnose, and to teach students the use of instruments which he could not use himself! Since then a change has come over medicine . . . The body is parcelled out among specialists as "claims" are "pegged out" by miners. Each orifice has, as an eminent surgeon said, a number of workers buzzing about it like flies'.



Sir John Herbert Parsons (1868-1957)
C.B.E., L.LD., D.SC., F.R.C.S., F.R.S.

D'Arcy Power, F.R.C.S., Surgeon to, and Lecturer on Surgery at, St. Bartholomew's Hospital, begins his article 'Some Cases of Chronic Ulceration of the Rectum' on a refreshingly original note: 'I have recently had under my care . . . several patients who have suffered from chronic ulceration of the rectum, and I found myself so ignorant of the causes and classification of this condition as to make it worth while to devote more attention to it than I had hitherto done'.

Stovaine was first employed in spinal anæsthesia by Henri Chaput in 1905. Lawrie McGavin, F.R.C.S., Surgeon to the Seamen's Hospital, and Gwynne Williams, F.R.C.S., Surgical Registrar, present 'A Report on 250 Cases of Spinal Analgesia by the Use of Stovaine-Glucose Solution': 'The method being but a special branch of the science of anæsthetics, its administration and investigation should be undertaken by the anæsthetist rather than the surgeon, and especially so since at times its application may fail from various

causes and necessitate the administration of a general anæsthetic'.

C. Paget Lapage, M.D., M.R.C.P., Physician to the Manchester Children's Hospital, discussing 'The Diagnosis of Permanent Mental Deficiency in Infancy and Childhood', states that in England and Wales alone there are 140,000 persons suffering from original mental defect—a proportion of 1 to 248 of the population. Charles Paget Lapage (1879-1947) was elected physician to the Children's Hospital, Pendlebury, in 1908, and five years later physician to children at the St. Mary's Hospitals, and from 1931 till 1947 he was reader on diseases of children at Manchester University. His book, 'Feeblemindedness in Children of School Age', published in 1911, became a classic.

In his paper, 'The Medical Inspection and Treatment of School Children', Clement Dukes, M.D., F.R.C.P., Consulting Physician to Rugby School, writes: 'Many of the parents . . . are quite able to pay for the services of their own medical advisers to carry out the necessary medical treatment of their children. In instances where such is not the case, if the State is to undertake the treatment of the remainder, adequate remuneration should be made by the State to local medical practitioners. . . . To attempt to make indiscriminate use of hospitals, which are charitable institutions . . . is incompatible with expediency in the public interest, or justice, either to the hospitals concerned, or to the gratuitous services of the honorary staff'. Clement Dukes (1845-1925) served as medical officer at Rugby School from 1871 to 1908, under four headmasters, and was the author of 'Health and School' (1887). A specialist in skin diseases, he described the fourth disease in 1900.

Among the books reviewed this month are 'Selections from the Writings of the late Sir William Broadbent, Bart', edited by Walter Broadbent; 'Electrical Treatment' by Wilfred Harris; 'Intercellular Enzymes' by H. M. Vernon ('well written, accurate, interesting, and very suggestive'); and 'The Pathology of the Eye. Vol. IV' by J. Herbert Parsons. Sir John Herbert Parsons, who died on October 7, 1957, in his 90th year, was educated at Bristol and at St. Bartholomew's Hospital, and took the B.Sc. with honours in physiology in 1890 and the F.R.C.S. in 1900. In 1904 he was elected to the surgical staff of 'Moorfields'. His monumental treatise in four volumes, 'The Pathology of the Eye' (1904-8), won him world-wide recognition. A brilliant, forceful personality and an original thinker, he served as president of the Ophthalmological Society of the United Kingdom in 1925 and as president of the Royal Society of Medicine in 1936-38. He was knighted in 1922.

W. R. B.

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